VOLUME 68 *November, 1953* NUMBER 5

THE AMERICAN REVIEW OF TUBERCULOSIS

A Journal of Pulmonary Diseases

OFFICIAL JOURNAL OF AMERICAN TRUDEAU SOCIETY
MEDICAL SECTION OF NATIONAL TUBERCULOSIS ASSOCIATION

CONTENTS

Bronchial Disease in Lungs Resected for Pulmonary Tuberculosis. DONALD E. OLSON, FRANCIS S. JONES, AND D. MURRAY ANGEVINE 657
Tuberculin Sensitivity and Contact with Tuberculosis. Further Evidence of Nonspecific Sensitivity. CARROLL E. PALMER 678
The Occurrence of Pulmonary Lesions in BCG-Vaccinated and Unvaccinated Persons. SAMUEL C. STEIN AND JOSEPH D. ARONSON 695
The Correlation of the Tuberculin Reaction with Roentgenographically Demonstrable Pulmonary Lesions in BCG-Vaccinated and Control Persons. JOSEPH D. ARONSON AND CHARLOTTE FERGUSON ARONSON 713
Cultural Properties of *M. Tuberculosis* in Resected Pulmonary Lesions of Patients Treated with Streptomycin and Para-Aminosalicylic Acid. GEORGE E. GRANVILLE, DANIEL E. JENKINS, DENTON A. COOLEY, MICHAEL E. DEBAKEY, FRANCIS C. WHITCOMB, AND BÉLA HALPERT 727
Susceptibility to Isoniazid and Pathogenicity of Tubercle Bacilli. HUBERT BLOCH, DANIEL WIDELOCK, AND LENORE R. PEIZER 734
Observations on the Serology of Pulmonary Tuberculosis. A. RICHARDSON JONES AND K. F. W. HINSON 739
Studies of Cellular Lysis in Tuberculin Sensitivity. BYRON H. WAKSMAN 746
Bronchography with a Water-Soluble Contrast Medium (Umbradil). SOL KATZ, PATRICK B. STOREY, GEORGES F. MCCORMICK, HECTOR PALACIOS, AND ANGEL DELEON PENSO 760
Case Reports:
Cardiac Involvement in Miliary Tuberculosis. HSIANG-LEN TSENG AND F. ROULET 771
Mechanism of Mediastinal Emphysema Complicating Therapeutic Pneumoperitoneum. J. WINTHROP PEABODY, JR. AND HOWARD A. BUECHNER 775
Editorial: The Problem of Tuberculosis in Psychotics. ABRAHAM M. BALTER, MICHAEL PILPEL, HAROLD S. HATCH, AND GEORGE N. J. SOMMER, JR. 782
Notes:
Results with Oxidation-Reduction Dyes in the Determination of Virulence of *Mycobacteria*. MARY E. CLARK AND ELIZABETH S. FORREST 786
A New Multipurpose Magnifying X-ray Viewer. EMANUEL SALZMAN 788
Unsuccessful Clinical Trials of Para-Isobutoxybenzaldehyde Thiosemicarbazone as an Antituberculous Drug in Man. CARL MUSCHENHEIM *et al.*; WILLIAM R. BARCLAY *et al.*; EDWARD M. GARMENT *et al.*; JOSEPH J. SAIA *et al.* 791
Books 803
American Trudeau Society:
The Award of the Trudeau Medal for 1953 808
Report of the Committee on Medical Research, 1952–1953 812
Report of the Fellowship Board of the Committee on Medical Research, 1952–1953 816
Present Concepts of Antimicrobial Therapy in Pulmonary Tuberculosis 819
Notes 837
Abstracts 93

Published Monthly at Mount Royal and Guilford Avenues, Baltimore 2, Maryland, by the National Tuberculosis Association • Business Off., 1790 Broadway, New York 19, N.Y.

Copyright 1953, by the National Tuberculosis Association

PRINTED IN U.S.A.

THE AMERICAN REVIEW OF TUBERCULOSIS

OFFICIAL JOURNAL OF AMERICAN TRUDEAU SOCIETY
Medical Section of National Tuberculosis Association

EDITOR
WALSH McDERMOTT
New York, N. Y.

CONSULTING EDITOR
ESMOND R. LONG
Philadelphia, Pa.

EDITOR OF ABSTRACTS
LAWRENCE B. HOBSON
New York, N. Y.

Helen W. Miller, *Editorial Secretary*

EDITORIAL BOARD

William H. Feldman, D.V.M., Rochester, Minn. Donald L. Paulson, M.D., Dallas, Tex.
Byron F. Francis, M.D., Seattle, Wash. Sidney Raffel, M.D., Stanford, Calif.
Daniel E. Jenkins, M.D., Houston, Tex. Philip E. Sartwell, M.D., Baltimore, Md.
Max B. Lurie, M.D., Philadelphia, Pa. John W. Strieder, M.D., Brookline, Mass.
Ralph Tompsett, M.D., New York, N.Y.

BUSINESS MANAGER
HENRY W. STEVENS

NOTICE TO SUBSCRIBERS AND CONTRIBUTORS

THE AMERICAN REVIEW OF TUBERCULOSIS is published by the National Tuberculosis Association and issued monthly about the first of the month. THE AMERICAN REVIEW OF TUBERCULOSIS is the official journal of the American Trudeau Society. A volume includes six numbers and begins with the January and July numbers.

Subscription: The subscription price of the REVIEW is $12 for the calendar year. Checks should be made payable to Collier Platt, Treasurer. The price of single copies is $1.50 postpaid.

Character of the Review: The REVIEW invites the submission of original manuscripts on any phase of tuberculosis, nontuberculous pulmonary diseases, and related subjects of interest.

MANUSCRIPTS

Contributors are requested to pay particular attention to the following rules governing the preparation of manuscripts. Failure to follow these rules is a frequent cause of delay in the publication of articles.

Manuscripts should be sent in duplicate to the office of the Editor, Dr. Walsh McDermott, 1790 Broadway, New York 19, N. Y., mailed flat, and transmitted by first-class mail with postage for return if not acceptable. They should be in English, double-spaced, typewritten on one side of the page with wide margins. Tabular data should not be included in the text but should be presented in separate tables with appropriate reference in the text. All cases of pulmonary tuberculosis should be classified according to the 1950 edition of *Diagnostic Standards and Classification of Tuberculosis* published by the National Tuberculosis Association. All case reports should be written in complete sentences. Authors should exercise particular care in the preparation, notation, and description of figures and tables. The form of reference used in the REVIEW should be carefully followed and references should be checked for accuracy. Each table must be accompanied by a descriptive title and a suitable legend must be provided for each figure. Drawings must be made with india ink and all lettering should be made with a stencil. The quality of the reproduction of a roentgenogram depends upon both the quality of the original picture and of the glossy print obtained from photographing that picture. If a contributor does not have facilities available, preparation of figures or reproduction of roentgenograms may be handled through the REVIEW office. In those circumstances, the contributor should supply a neat, properly proportioned, and suitably entitled drawing or the original roentgenogram, and will be expected to defray the cost of these services.

The publishers will not be responsible for manuscripts, illustrations, etc., lost in transit. In order to save expense for authors' corrections in proof, manuscripts should be carefully revised by the author before submission.

Reprints: Fifty reprints without covers of articles will be furnished to authors free of charge when requested in advance. Additional reprints may be ordered.

Advertising: Rates will be furnished by THE AMERICAN REVIEW OF TUBERCULOSIS, 1790 Broadway, New York 19, N. Y. on request.

The Publishers reserve the right to decline any advertising submitted and to censor all copy. Acceptance of an advertisement does not constitute official endorsement of the product advertised.

Entered as second-class matter March 9, 1917, at the post office at Baltimore, Md., under the Act of August 24, 1912. Acceptance for mailing at a special rate of postage provided for in section 1103, Act of October 3, 1917. Authorized on July 2, 1918.

When Fever Persists . . .

. . . physicians often prescribe one or more Pulvules 'Becotin with Vitamin C' a day. This potent formula provides, in one pulvule, a *therapeutic dose of all the better-known water-soluble vitamins.*

Each pulvule contains:

Thiamin Chloride	10	mg.
Riboflavin	10	mg.
Pyridoxine Hydrochloride	5	mg.
Nicotinamide	50	mg.
Pantothenic Acid (as Calcium Pantothenate)	25	mg.
Vitamin B_{12} (Activity Equivalent)	1	mcg
Ascorbic Acid	150	mg.
Liver Preparation and Stomach-Tissue Material, Desiccated, Lilly	0.39	Gm.

Eli Lilly and Company
Indianapolis 6, Indiana, U. S. A.

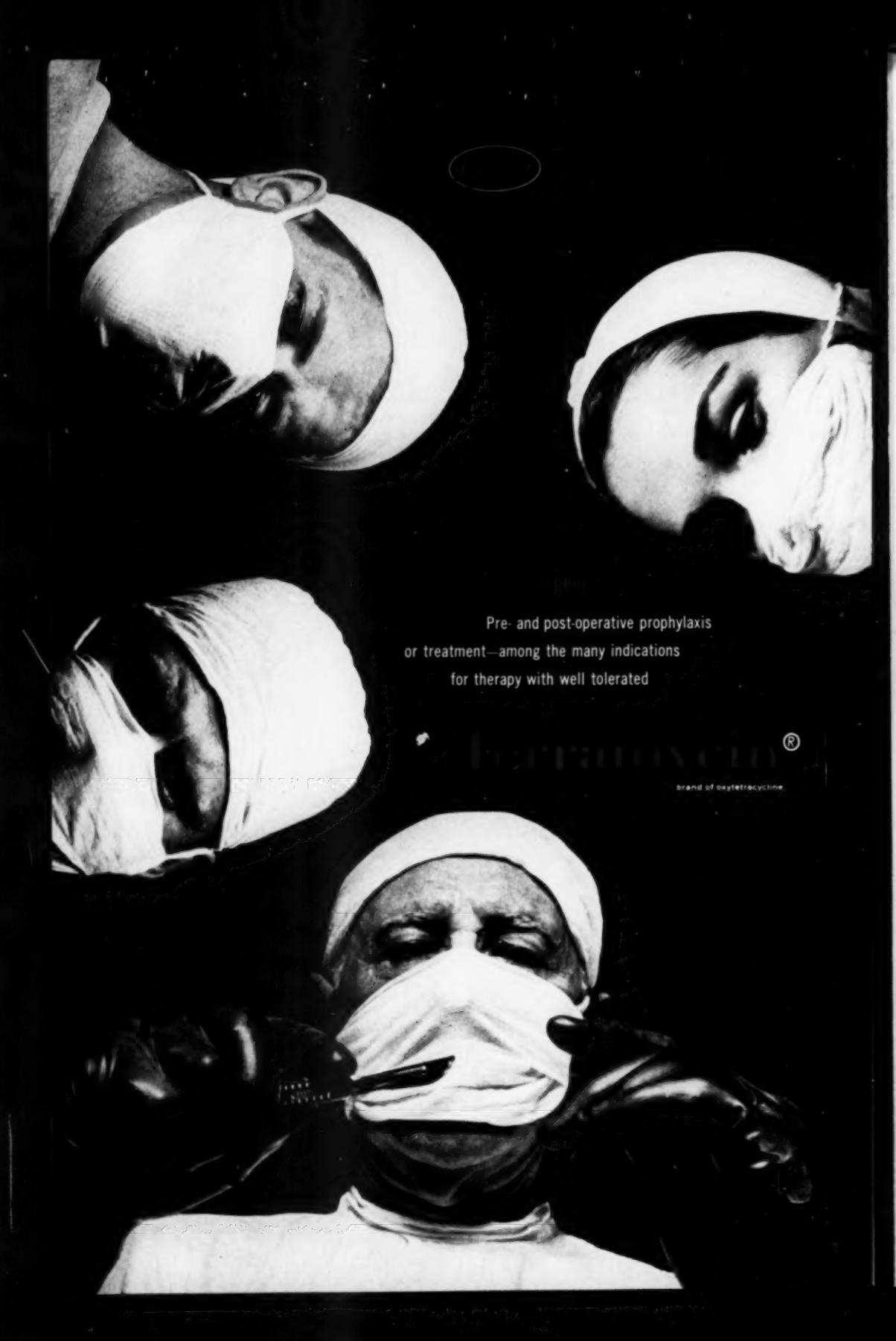
Lilly

For metabolic support in febrile diseases prescribe

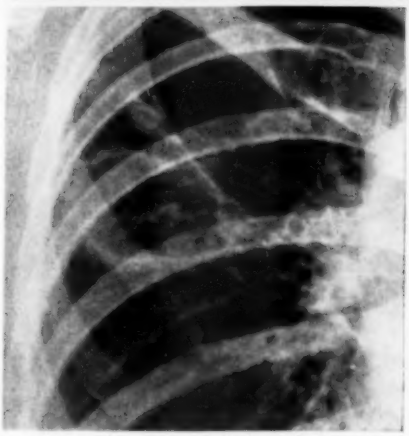
PULVULES

'Becotin with Vitamin C'

(VITAMIN B COMPLEX WITH VITAMIN C, LILLY)


Pre- and post-operative prophylaxis
or treatment—among the many indications
for therapy with well tolerated
®
brand of oxytetracycline

Suspected?



Conventional six-foot chest

Revealed!

ORDOGRAPH film — same area

Body-section radiography facilitates accurate diagnosis of difficult-to-define areas

In conventional radiography, a definite diagnosis often cannot be made because of anatomical superimposition. And, though special views are taken (obliques, tangential shots or stereos), the suspected pathology still may defy conclusive interpretation. In such cases, body-section radiography quickly isolates the pathological area.

The GE ORDOGRAPH is the only table-attached apparatus that provides complete facilities. Whether the x-ray table is horizontal or vertical, ORDOGRAPH offers body-section technics with the patient standing, sitting, lying or in decubitus positions.

More — the exclusive GE hydraulic drive is the only method that assures smooth traversal of tube stand and Bucky. Its two-minute change-over eliminates special scheduling — makes body-section radiography a routine procedure. And, because it occupies otherwise unused space, the ORDOGRAPH is always ready for use without interfering with other diagnostic technics.

For complete information on the ORDOGRAPH, as well as an explanatory booklet, "Body-Section Radiography," see your GE x-ray representative. Or write X-Ray Department, General Electric Company, Milwaukee 1, Wis., for Pub. S-11.

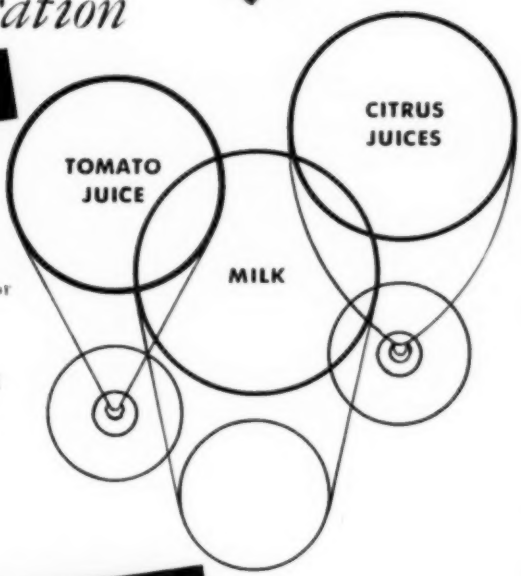
You can put your confidence in —

GENERAL ELECTRIC

In Tuberculosis Therapy Choose The Most Versatile- Most Convenient- Most Accurate Method of PAS Administration

Hellwig's PACKETTES

With Hellwig's PACKETTES the preparation of a single dose of P.A.S. no longer entails measuring powder or counting tablets. No chance of inaccuracy. Each envelope is pre-weighed. Each PACKETTE contains 4.18 grams of *neutral* Sodium Para amino Salicylate Dihydrate (4.18 grams being equal to exactly 3.0 grams of *free* Para amino Salicylic Acid).



50 PACKETTES IN A BOX

Also available in Junior Size for Children —

Hellwig, Inc.

209 E. Chestnut St. Chicago, Illinois

Saranac Lake, N. Y.

New principle in Streptomycin Therapy

The hazard of ototoxicity is greatly reduced by combining equal parts of streptomycin sulfate and dihydrostreptomycin sulfate. The patient thus gets only *half* as much of each drug. The risk of vestibular damage (from streptomycin) and of hearing loss (from dihydrostreptomycin) is greatly reduced. Therapeutic effect is undiminished. This principle has been demonstrated in both animals and man. In patients treated for 120 days with 1 Gm. per day of the combined drugs, the incidence of neurotoxicity was practically zero.

Cat treated with streptomycin is ataxic.

Cat treated with the same amount of streptomycin-dihydrostreptomycin has normal equilibrium.

DISTRYCIN
(di-STRI-sin)

Squibb Streptomycin Sulfate *and* Dihydrostreptomycin Sulfate in equal parts

FOR GREATER SAFETY IN COMBINED ANTIBIOTIC THERAPY

These new formulations embody this new principle:

	DISTRYCIN	DICRYSTICIN	DICRYSTICIN FORTIS	DISTRYCILLIN A.S.
Streptomycin sulfate, Gm.	0.5	0.25	0.5	0.25
Dihydrostreptomycin sulfate, Gm.	0.5	0.25	0.5	0.25
Procaine penicillin G, units	—	300,000	300,000	400,000
Potassium penicillin G, units	—	100,000	100,000	—

(All supplied in 1 and 5 dose vials)

'Distrycin' and 'Dicrysticin' are registered trademarks; 'Distrycillin' is a trademark.

SQUIBB
a leader in the research and manufacture of penicillin and streptomycin

PRECISION INSTRUMENTS FOR THORACIC SURGERY
Made by PILLING

RUSTLESS STAINLESS STEEL MADE IN U.S.A.

Reading clockwise:

GIERTZ-SCHOEMAKER RIB SHEARS
Th 555 Length 10", $60.00 each.

SEMB RIB SHEARS
Th 580 Length 10½", $66.95 each.

SAUERBRUCH-FREY RIB SHEARS
Th 590 Length 15", adult size, $82.40 each.

LEBSCHE STERNUM CHISEL
Th 620 Length 10", $22.35 each.

SAUERBRUCH DOUBLE ACTION RIB RONGEUR
Th 675 Length 12", curved jaws, 17 mm. square bite, $66.95 each.
Th 685 Length 12", curved jaws, 17 mm. round bite, $66.95 each.

SEMB RIB RONGEUR
Th 705 Length 10", $66.95 each.

Headquarters for Thoracic Instruments

Order direct from:
GEORGE P. Pilling & SON CO.
3451 WALNUT STREET • PHILADELPHIA

New Safety in long-term

Streptomycin Therapy

The incidence of auditory and vestibular disturbances is lessened following therapy with DUO-STREP.

DUO-STREP greatly reduces the possibility of toxic effects that may occur from prolonged daily therapy with streptomycin or dihydrostreptomycin. Yet, DUO-STREP provides full therapeutic efficacy. These advantages are assured by the composition of DUO-STREP: each dose contains half the usual dose of streptomycin and half the usual dose of dihydrostreptomycin. Patients receive full therapeutic benefit with sharply diminished ototoxic hazard.

DUO-STREP

(Trade-mark)

SUPPLIED: In vials of 1 and 5 Gm., each gram composed of 0.5 Gm. Streptomycin Sulfate and 0.5 Gm. of Crystalline Dihydrostreptomycin Sulfate.

Research and Production for the Nation's Health

MERCK & CO., INC.
Manufacturing Chemists
RAHWAY, NEW JERSEY

© Merck & Co., Inc.

A new form of a synthetic narcotic analgesic . . . approximately twice as potent as racemic Dromoran (dl) Hydrobromide 'Roche' . . . inducing prompt pain relief with longer duration of analgesic effect than morphine.

. . . indicated for the relief of severe or intractable pain . . . preoperative medication and postoperative analgesia.

. . . "A striking characteristic is its ability to produce cheerfulness in pain-depressed patients the morning after an evening dose."*

. . . less likely than morphine to produce constipation, nausea or other undesirable side effects . . . whether administered orally or subcutaneously.

LEVO-DROMORAN

TARTRATE *'Roche'*

(tartaric acid salt of levo-3-hydroxy-N-methylmorphinan)

CAUTION.
Levo-Dromoran Tartrate is a narcotic analgesic. It has an addiction liability equal to morphine and therefore the same precautions should be taken in dispensing this drug as with morphine.

*Glazebrook, A. J.: Brit. M. J., 2:1328 (Dec. 20) 1952.

HOFFMANN-LA ROCHE INC. • Nutley 10 • New Jersey

LEVO-DROMORAN®—brand of levorphan

THE AMERICAN REVIEW
OF
TUBERCULOSIS
A Journal of Pulmonary Diseases

VOLUME 68 | *November, 1953* | NUMBER 5

BRONCHIAL DISEASE IN LUNGS RESECTED FOR PULMONARY TUBERCULOSIS[1, 2, 3]

DONALD E. OLSON, FRANCIS S. JONES, AND D. MURRAY ANGEVINE

(Received for publication July 27, 1953)

INTRODUCTION AND REVIEW OF LITERATURE

The clinical importance of bronchial disease in pulmonary tuberculosis has long been recognized. Symptoms such as cough, expectoration, hemoptysis, wheezing, "asthmatic attacks," dyspnea, and cyanosis may be attributed solely to bronchial abnormalities in many tuberculous subjects (1–4). In those patients with minimal noncavitary parenchymal infiltrates, it has been assumed that tuberculous foci within the bronchial wall were the source of sputum positive for tubercle bacilli. Furthermore, endobronchial lesions have been implicated when extensions of the tuberculous process have occurred in previously well-controlled noncavitary disease (5, 6). Atelectasis, blocked cavities, and obstructive emphysema in tuberculosis have been considered as secondary to bronchial changes (4, 6, 7–13). Prior to the use of chemotherapy, known endobronchial tuberculosis carried a serious prognosis. The results of pneumothorax were notoriously poor, and thoracoplasty was not as successful in the presence of known endobronchial tuberculosis (8, 14–19). When grossly involved tuberculous bronchi have been divided and closed during pulmonary resections, the incidence of major postoperative complications has been high (20). Such clinical observations have been the impetus for numerous investigations of the bronchi in tuberculous subjects.

The advent of bronchography furnished a convenient and frequently utilized method for visualizing the contour of the bronchial tree. By this technique, Jones, Peek, and Willis (13) and Blair and Roberts (21) have demonstrated a 70 and 92 per cent incidence, respectively, of residual bronchiectasis in segments which had been collapsed for extended periods. Buckles and co-workers (22) and Rabinowitz and Harper (23) have shown that 54 and 83 per cent, respectively,

[1] From the Departments of Medicine and Pathology, University Hospitals, University of Wisconsin Medical School, and the Veterans Administration Hospital, Madison, Wisconsin.

[2] Presented in part before the Medical Session, as part of the session on *Surgery in the Treatment of Pulmonary Diseases* at the annual meeting of the National Tuberculosis Association, Los Angeles, California, on May 21, 1953.

[3] This study was supported by a research grant from the Wisconsin Antituberculosis Association.

of their patients had abnormal bronchograms. Employing bronchographic techniques on 100 autopsy specimens, Jones and associates (24) reported that 51 had bronchiectasis; furthermore, the bronchiectasis was much more prevalent in association with fibrotic disease of long known duration.

In the majority of studies, ectatic bronchi were primarily located in the areas of parenchymal tuberculosis. Usually the apical-posterior segments of the upper lobes and the superior segments of the lower lobes were affected (23). Isolated bronchiectasis of the basal segments of the lower lobes was detected rather infrequently (22, 23, 25). Moreover, Gordon, Brook, and Pratt (26) have contended that bronchiectases, associated with pulmonary tuberculosis, is confined to the medial two-thirds of the lung. This has been contradicted, however, by Jones and associates (13) who found dilated bronchi extending to the periphery.

Although bronchography has furnished data on the distortion and caliber of bronchi, it has not provided information concerning mucosal lesions of specific etiology. Bronchoscopy has bridged this gap to a limited extent. Wilson (6) performed bronchoscopy routinely on patients recently admitted to a sanatorium and found that 10 to 15 per cent had visible endobronchial tuberculous disease. Numerous other bronchoscopic studies reported by MacRae and co-workers (27), Myerson (28), Overholt and Wilson (29), Buckles and Neptune (15), and Rabinowitz and Harper (23) have shown an incidence of endobronchial lesions varying between 14 and 31.7 per cent. Recently, a British Tuberculosis Association Research Committee (30) has tabulated bronchoscopy data from six hospitals and found that the percentage of abnormal findings varied from 18 to 85 per cent, with an average of 34 per cent. The Committee could not find a correlation of endobronchial tuberculosis with the patients' age, sex, or known duration of disease.

Detailed and specific data on tuberculous involvement of the bronchi have been obtained from examination of both autopsy and surgical tissues. Most specimens have been obtained from patients with far advanced pulmonary tuberculosis who had received little or no chemotherapy. In studies in which only bronchial stumps of surgical specimens were examined, 10 to 35 per cent (31, 32) showed tuberculous lesions. In studies in which the trachea and main stem bronchi have been examined, the incidence of tuberculous endobronchitis has varied from 35.4 to 60 per cent (4, 14, 24, 33-36, 40). In studies of both surgical and autopsy material, in which segmental or smaller bronchi were examined, the incidence of tuberculous endobronchitis tended to increase from 52 to 80 per cent or more (5, 15, 16, 22, 29, 32, 37). It has been comparatively rare to find tuberculous endobronchitis independent of parenchymal involvement (7).

Relatively little data are available on the incidence of endobronchial tuberculosis and bronchiectasis associated with minimal and moderately advanced cases of pulmonary tuberculosis. Furthermore, there are no significant data on the effect of prolonged streptomycin para-aminosalicylic acid (PAS) therapy on these entities.

The present study is based on a relatively large number of surgically resected pulmonary tissues obtained from patients, many of whom had received prolonged

streptomycin-PAS therapy and had only minimal or moderately advanced disease. In the present material, the incidence of certain bronchial diseases has been determined and correlated with the types of parenchymal tuberculosis and clinical data.

MATERIALS AND METHODS

Six hundred and fifty-eight consecutive surgical specimens resected from patients with pulmonary tuberculosis at the University Hospitals and Veterans Administration Hospital, Madison, Wisconsin between December, 1948, and November 1, 1952 have been examined.

After surgical excision, the specimens were promptly reinflated whenever possible to approximately normal volume by injection of the bronchial tree with air and Kaiserling's solution or 10 per cent formalin and were then immersed in fixative. Subsequently, the specimens were sectioned coronally to the hilum into 0.5 to 1.0 cm. slices. Multiple blocks of tissue, which included the representative parenchymal tuberculous foci plus their associated and draining bronchi, were removed from each specimen for microscopic examination. In addition, blocks of the bronchi were taken for examination from 302 specimens at or near the margin of excision. All tissue sections were stained with hematoxylin and eosin.

Each specimen in which the bronchi could be adequately evaluated was classified in only one of the five following categories:

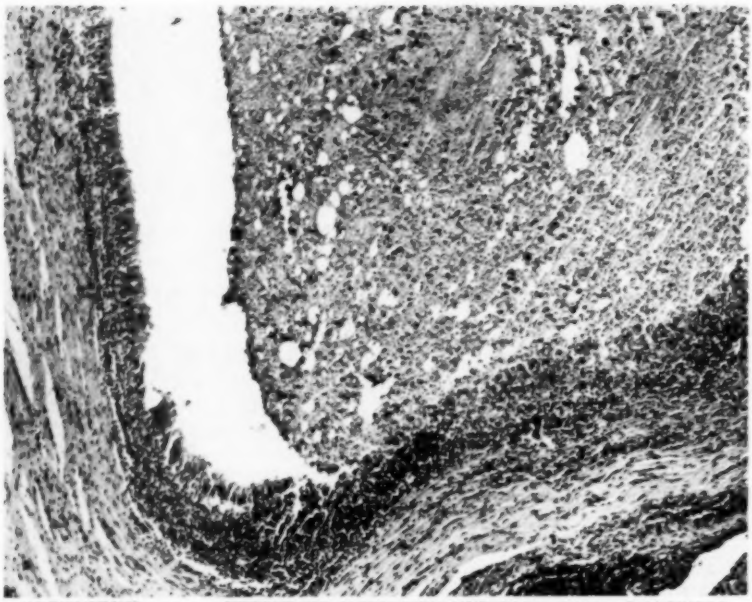
(*1*) bronchi normal, (*2*) chronic bronchitis, (*3*) tuberculous bronchitis, (*4*) bronchiectasis without endobronchial tuberculosis, and (*5*) bronchiectasis with endobronchial tuberculosis.

No attempt was made to evaluate the extent or severity of these conditions. In those specimens in which sections were obtained from the hilum, the presence or absence of hilar endobronchial tuberculosis was separately tabulated. A separate record of complete or partial gross bronchial stenosis also was made.

A diagnosis of bronchiectasis was made only when gross dilatation and distortion of the bronchi were readily discernible. If tubercles, caseation, or tuberculous granulation tissue were found in any portion of the dilated bronchial wall, the specimen was classified as bronchiectasis with endobronchial tuberculosis (figures 1 and 2). If no tuberculous lesions were demonstrated within the bronchial wall, the specimen was classified as bronchiectasis without endobronchial tuberculosis. When bronchi of normal caliber contained tuberculous foci within the wall, a diagnosis of tuberculous bronchitis was made (figures 3 and 4). The diagnoses of tuberculous bronchitis or bronchiectasis with endobronchial tuberculosis were not made if the sole lesion was at a bronchocavitary junction. Chronic bronchitis was defined as a significant increase in lymphocyte and plasma cell infiltration of the bronchial wall without evidence of specific tuberculous lesions.

RESULTS

The histopathology of endobronchial tuberculosis varied in extent and severity. Principally, the lesions were confined to the submucosal area, but in a moderate number of specimens the tuberculous infection had infiltrated bronchial glands and cartilage, as well as the adventitia and smooth muscle. The smallest foci were composed almost entirely of epithelioid and Langhans' giant cells. As the lesions increased in size, central caseation was noted, and the overlying respiratory epithelium usually revealed squamous metaplasia. When a tuberculous ulcer had formed, the base was composed of fibrous tissue and lymphocytes covered by a layer of tuberculous granulation tissue. The inner layer was com-



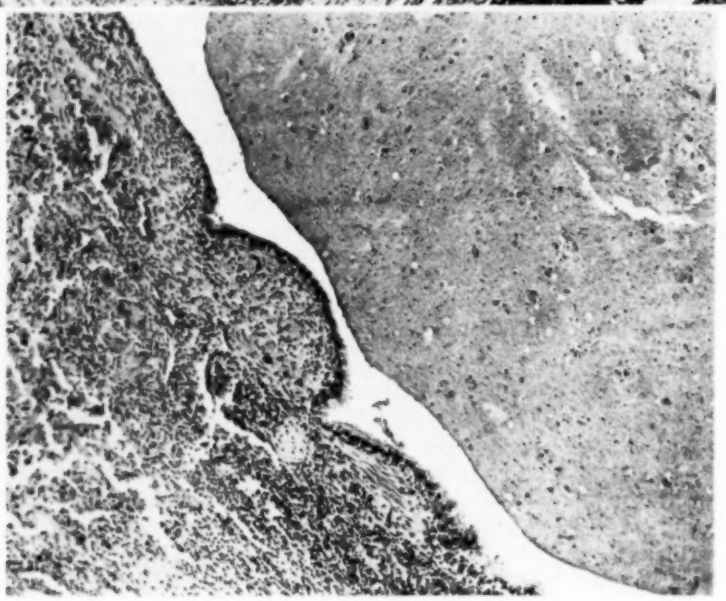


FIG. 1 (Top). Tuberculous bronchiectasis. Large mononuclear cells are present at the site of the epithelial ulceration. There is a dense fibrous wall and the dilated lumen contains much exudate. (×60)

FIG. 2 (Bottom). Tuberculous bronchiectasis. A small cellular tubercle with giant cells is present beneath the epithelium of a cystically dilated bronchus. Mucus fills the bronchial lumen. (×60)

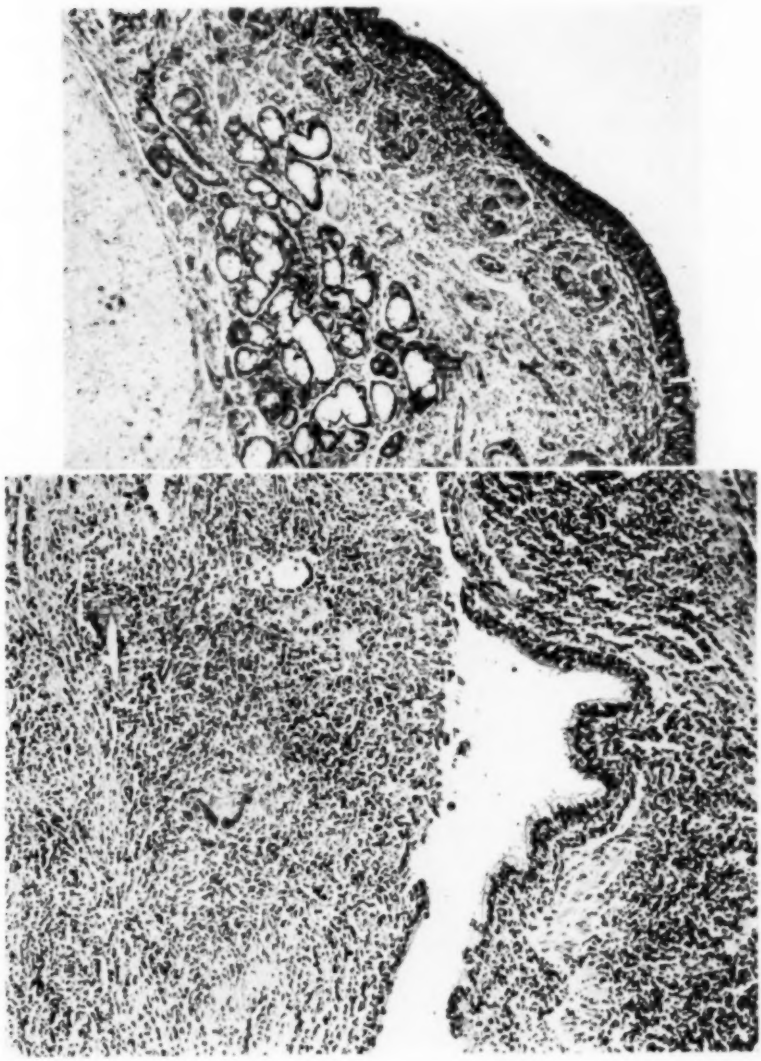


FIG. 3 (Top). Tuberculous bronchitis. Several small cellular tubercles are present in the subepithelial connective tissue of a large bronchus (×200.)

FIG. 4 (Bottom). Tuberculous bronchitis. There is ulceration of the epithelium and marked chronic inflammatory cell infiltration of the wall of a small bronchus. Giant cells are frequent. (×200)

posed of caseous material, cellular debris, and polymorphonuclear leukocytes. At the margin of such ulcers, squamous metaplasia of the bronchial epithelium had occurred in most instances. In addition to the tuberculous involvement, the bronchi have usually shown moderate to marked lymphocyte and plasma cell infiltration of the submucosa and the stroma around the bronchial glands. Ordinarily, the ectatic bronchi had fibrous thickening of the wall which replaced smooth muscle and the normal structure of the submucosa. Fibrosis and dilatation were commonly accompanied by some degree of submucosal infiltration with lymphocytes and plasma cells. When tuberculous endobronchial lesions occurred in association with bronchiectasis, the histopathology was similar to that of "tuberculous bronchitis." When bronchial abnormalities were found, the bronchial vessels usually showed some thickening of the intima and adventitia. Osseous metaplasia of the bronchial cartilages was occasionally observed, and three specimens contained broncholiths.

TABLE 1

THE INCIDENCE OF VARIOUS TYPES OF BRONCHIAL DISEASES IN 602 SURGICAL SPECIMENS REMOVED FROM PATIENTS WITH PULMONARY TUBERCULOSIS

	NUMBER	PER CENT
Bronchi normal	57	9.5
Chronic bronchitis	173	28.7
Tuberculous bronchitis	121	20.0
Bronchiectasis without endobronchial tuberculosis	129	21.4
Bronchiectasis with endobronchial tuberculosis	122	20.3
Total with bronchiectasis	251	41.7
Percentage of bronchiectatic specimens with endobronchial tuberculosis		48.6
Total specimens with endobronchial tuberculosis	243	40.3

In 602 of the 658 specimens, gross and microscopic material was considered adequate for a complete appraisal of the pathology. The following data are based on these 602 specimens unless otherwise specifically noted. The incidence of the types of bronchial disease is given in table 1.

Incidence of abnormalities: It is worthy of note that in only 10 per cent[1] of the specimens were the bronchi considered normal. Of the 251 bronchiectatic specimens, 49 per cent had associated endobronchial tuberculosis. Of the 602 specimens, 40 per cent had some degree of endobronchial tuberculosis. Furthermore, it was found that 38 specimens had gross hilar bronchial stenosis, and 33 of the 302 specimens in which the hilar bronchi were examined microscopically revealed tuberculous lesions. Only 4 specimens had bronchiectasis with endobronchial tuberculosis unassociated with significant parenchymal disease. Of the 658 total specimens, 31 had tuberculosis of the hilar lymph nodes.

Nature of parenchymal lesions: For comparative purposes, the parenchymal lesions were divided into many categories. Each specimen was first classified

[1] Percentages given in the text are recorded in whole numbers.

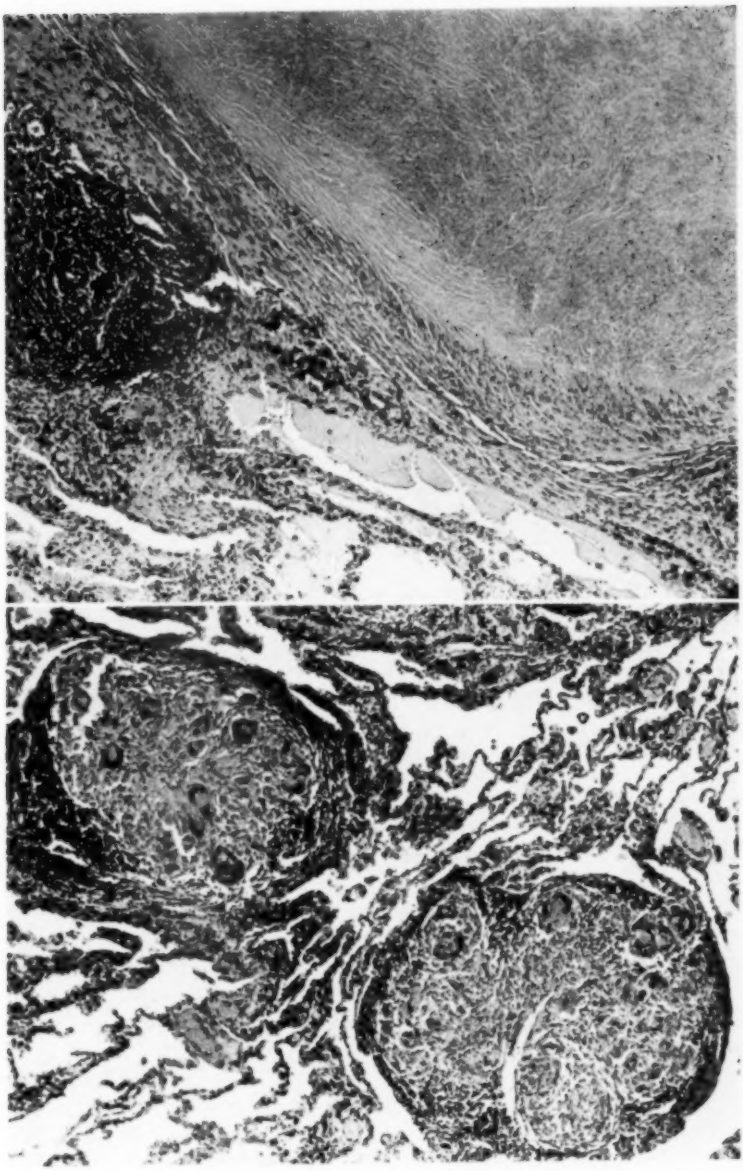


FIG. 5 (Top). Fibrocaseous nodule. The central area of caseation is surrounded by zone of dense fibrous tissue. A focal collection of lymphocytes is also present. (×60)

FIG. 6 (Bottom). Cellular tubercles. Although there are beginning fibrosis and a peripheral zone of lymphocytes, the lesions are composed mostly of large mononuclear "epithelioid" cells and giant cells. (×80)

according to its dominant type of "solid" tuberculous parenchymal nodule. One hundred and ninety-three specimens had predominantly fibrocaseous nodules with moderately to markedly thickened fibrous, relatively acellular walls, and central caseation (figure 5). In contrast were 104 specimens with "cellular" tubercles which were characterized by abundant epithelioid and Langhans' giant cells with minimal evidence of caseation and/or fibrosis (figure 6). Mixtures of these two types of lesions were found in 299 specimens.

TABLE 2

A Comparison of Certain Parenchymal Lesions with the Type of Bronchial Disease in the Specimens

	Fibrocaseous nodules		Cellular tubercles		Fibrocaseous nodules and cellular tubercles	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Bronchi normal	30	15.5	5	4.8	22	7.4
Chronic bronchitis	71	36.8	17	16.3	83	27.8
Tuberculous bronchitis	7	3.6	48*	46.2	66*	22.1
Bronchiectasis without endobronchial tuberculosis	70	36.3	4	3.8	55	18.4
Bronchiectasis with endobronchial tuberculosis	15	7.8	30*	28.8	73*	24.4
Both types of bronchiectasis	85	44.0	34	32.7	128	42.8
Total specimens with endobronchial tuberculosis	22	11.4	78*	75.0	139*	46.5
Total specimens in group	193		104		299	

* Statistically significant at the 1 per cent level.

The specimens containing predominantly cellular tubercles and a combination of fibrocaseous nodules and cellular tubercles were compared with those specimens containing only fibrocaseous nodules.

In table 2,[5] these parenchymal lesions are compared with the types of bronchial disease in the specimens. As compared with those specimens containing only fibrocaseous nodules, specimens with predominately cellular tubercles or a mixture of cellular tubercles and fibrocaseous nodules showed a statistically significant increase in endobronchial tuberculosis. Although there was no statistically significant difference in the incidence of bronchiectasis associated with any of the three varieties of nodules, there was a tendency for bronchiectasis to occur less frequently with "cellular" disease.

Because of the possible pathogenetic relationship between cavitary or liquefying parenchymal foci and endobronchial tuberculosis, each specimen was reclassified into only one of three groups: (*1*) gross cavity, (*2*) liquefying lesions, and (*3*) solid noncavitary and nonliquefying lesions.

As table 3 indicates, 150 specimens had grossly detectable cavitation. Of the

[5] The statistical analyses of the data were done by Dr. Preston Hammer and associates in the Department of Numerical Analysis, University of Wisconsin, Madison, Wisconsin

remaining specimens, 148 had one or more liquefying lesions in which the central part was partially or completely replaced by basophilic substance, cellular debris, and polymorphonuclear leukocytes (figure 7). The inner aspect of the fibrous capsule of these liquefying lesions usually was composed of tuberculous granulation tissue. Three hundred and four specimens contained only solid, noncavitary, nonliquefying nodular foci. There was a significant increase in the incidence of endobronchial tuberculosis in those specimens which contained a gross cavity as compared to those with liquefying or solid nodular lesions. Although there was a tendency for the incidence of bronchiectasis to increase in the specimens with solid nodular lesions, it was not statistically significant.

TABLE 3

A Comparison of Specimens Containing Cavitary, Liquefying, and Noncavitary Lesions with the Type of Bronchial Disease

	Gross cavity		Liquefying lesions		Noncavitary and nonliquefying lesions	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Bronchi normal	4*	2.7	12	8.1	41	13.5
Chronic bronchitis	38	25.3	46	31.1	89	29.3
Tuberculous bronchitis	51*	34.0	29	19.6	41	13.5
Bronchiectasis without endobronchial tuberculosis	17	11.3	30	20.3	82	27.0
Bronchiectasis with endobronchial tuberculosis	40†	26.7	31	20.9	51	16.8
Both types of bronchiectasis	57	38.0	61	41.2	133	43.8
Total specimens with endobronchial tuberculosis	91*	60.7	60	40.5	92	30.3
Total specimens in group	150		148		304	

* and† Statistically significant at the 1 per cent and 5 per cent levels, respectively.

The specimens containing gross cavities and liquefying lesions were compared with those specimens containing only noncavitary and nonliquefying lesions.

Pulmonary fibrosis independent of specific tuberculous lesions: The degree of interstitial pulmonary fibrosis independent of the specific tuberculous lesions was subjectively evaluated and graded according to severity. Of the 602 specimens, 91 had minimal, 309 had moderate, 191 had marked evidence of interstitial fibrosis (table 4), and in only 11 instances was it not detectable. The incidence of normal bronchi was significantly reduced, whereas the incidence of bronchiectasis was significantly augmented in those specimens with moderate to marked interstitial fibrosis. Endobronchial tuberculosis was not influenced by the degree of fibrosis.

Age and sex: In tables 5 and 6 the sex and age, respectively, of the patients are compared with the incidence of the bronchial diseases. There was no significant correlation between these clinical factors and bronchial abnormalities. However, there was a tendency for female patients to have a higher incidence of bronchiectasis and endobronchial tuberculosis than males.

Duration and extent of pulmonary disease: Initially, the known duration of the patients' illness was broken into multiple categories, but no essential difference in the incidence of bronchial lesions was noted except in the two large composite groups: those who had had tuberculosis for less than three years, and those who had had tuberculosis for three or more years (table 7). The incidence of bronchiectasis was significantly increased, but there was a tendency for the incidence of tuberculous bronchitis to decrease in the patients who had had recognized tuberculosis of long duration.

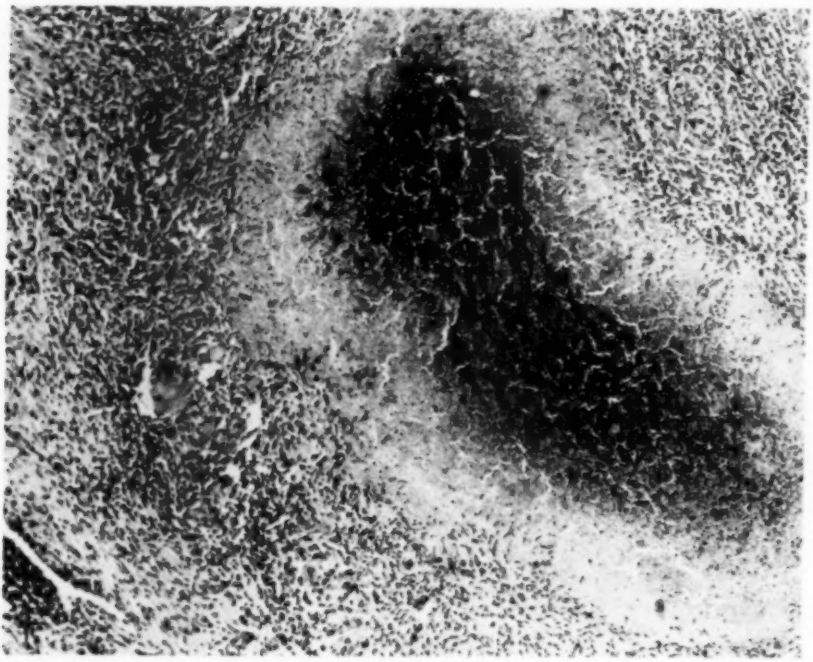


FIG. 7. Liquefying caseous lesion. The central portion of this lesion contains much nuclear debris as well as many intact polynuclear leukocytes. The wall of the lesion contains many inflammatory cells including several large giant cells. (×80)

As indicated in table 8, the specimens were obtained from 43 patients who had minimal, 282 who had moderately advanced, and 277 who had far advanced, pulmonary tuberculosis. The incidence of tuberculous endobronchitis increased progressively with the clinical extent of the disease, and the incidence of bronchiectasis was significantly elevated in the moderately advanced and far advanced cases as compared to the cases of minimal disease. A much larger percentage of the patients with minimal tuberculosis had normal bronchi than did those with more extensive disease. It also was found that specimens from patients who required lobectomy or pneumonectomy showed a significant increase in the

incidence of bronchiectasis and endobronchial tuberculosis when compared with those from patients on whom only segmental resections were done (table 9).

Comparison of bronchoscopic and pathologic examinations: Within a short period prior to surgery, bronchoscopy was performed on patients from whom

TABLE 4

A Comparison of the Degree of Interstitial Pulmonary Fibrosis with the Type of Bronchial Disease in the Specimens

	Fibrosis I		Fibrosis II		Fibrosis III	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Bronchi normal	19	20.8	24*	7.7	9*	4.6
Chronic bronchitis	29	31.8	92	29.7	49	25.6
Tuberculous bronchitis	21	23.7	65	21.0	34	17.8
Bronchiectasis without endobronchial tuberculosis	11	12.1	61	19.7	56	29.3
Bronchiectasis with endobronchial tuberculosis	11	12.1	67	21.7	43	22.5
Both types of bronchiectasis	22	24.2	128†	41.4	99*	51.8
Total specimens with endobronchial tuberculosis	32	35.8	132	42.7	77	40.3
Total specimens in group	91		309		191	

* and †. See table 3.

Fibrosis I, Fibrosis II, and Fibrosis III, respectively, indicate minimal, moderate, and marked degrees of interstitial fibrosis. The specimens containing moderate and marked interstitial fibrosis were compared with those specimens containing minimal fibrosis.

TABLE 5

A Comparison of the Sex of the Patients with the Type of Bronchial Disease

	Males		Females	
	Number	Per Cent	Number	Per Cent
Bronchi normal	31	9.6	26	9.4
Chronic bronchitis	103	31.8	70	25.2
Tuberculous bronchitis	62	19.1	59	21.2
Bronchiectasis without endobronchial tuberculosis	72	22.2	57	20.5
Bronchiectasis with endobronchial tuberculosis	56	17.3	66	23.7
Both types of bronchiectasis	128	39.5	123	44.2
Total specimens with endobronchial tuberculosis	118	36.4	125	45.0
Total specimens in group	324		278	

No statistically significant differences were found.

582 specimens were obtained. The bronchoscopy reports revealed 462 (79 per cent) with normal bronchi, 46 (8 per cent) with red or friable mucous membranes, 33 (6 per cent) with tuberculous bronchitis, and 41 (7 per cent) with bronchial stenosis (table 10). However, only 10 per cent of the specimens from patients with normal bronchoscopy had normal bronchi on histopathologic examination,

TABLE 6

A Comparison of the Age of the Patients with the Type of Bronchial Disease

	AGE											
	6–19		20–29		30–39		40–49		50–59		60–79	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Bronchi normal	2	8	21	10.4	11	6.2	11	10.1	8	13.3	4	14.3
Chronic bronchitis	8	32	69	34.2	54	30.5	25	22.9	14	23.3	3	10.7
Tuberculous bronchitis	8	32	36	17.8	32	18.1	24	22.0	16	26.7	5	17.9
Bronchiectasis without endobronchial tuberculosis	3	12	37	18.3	41	23.2	28	25.7	11	18.3	9	32.1
Bronchiectasis with endobronchial tuberculosis	4	20	39	19.3	39	22.0	21	19.3	11	18.3	7	25.0
Both types of bronchiectasis	8	32	76	37.6	80	45.2	49	45.0	22	36.7	16	57.1
Total specimens with endobronchial tuberculosis	13	52	75	37.1	71	40.1	45	41.3	27	45.0	12	42.9
Total specimens in group	25		202		177		109		60		28	

The 20- through 29-year age group was taken as the standard, and all other age groups were compared with it. No statistically significant differences were found.

TABLE 7

A Comparison of the Known Duration of the Patients' Tuberculosis with the Type of Bronchial Disease in the Specimens

	DURATION ONE MONTH TO THREE YEARS		DURATION THREE YEARS OR MORE	
	Number	Per Cent	Number	Per Cent
Bronchi normal	31	9.8	26	9.1
Chronic bronchitis	97	30.8	76	26.5
Tuberculous bronchitis	74	23.5	47	16.4
Bronchiectasis without endobronchial tuberculosis	55	17.5	74*	25.8
Bronchiectasis with endobronchial tuberculosis	58	18.4	64	22.3
Both types of bronchiectasis	113	35.9	138*	48.1
Total specimens with endobronchial tuberculosis	132	41.9	111	38.7
Total specimens in group	315		287	

* Statistically significant at the 5 per cent level.

whereas 40 per cent had bronchiectasis and 38 per cent had endobronchial tuberculous lesions. Although there was no statistically significant increase in the incidence of bronchiectasis and endobronchial disease in specimens from patients with abnormal bronchoscopies, there was a definite tendency for the incidence to rise.

TABLE 8

A Comparison of the Clinical Extent of the Patients' Tuberculosis with the Type of Bronchial Disease in the Specimen

	MINIMAL		MODERATE		FAR ADVANCED	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Bronchi normal	12	27.9	31*	11.0	14*	5.1
Chronic bronchitis	19	44.2	82	29.1	72	26.0
Tuberculous bronchitis	9	20.9	49	17.4	63	22.7
Bronchiectasis without endobronchial tuberculosis	0	0.0	71	25.2	58	20.9
Bronchiectasis with endobronchial tuberculosis	3	7.0	49	17.4	70†	25.3
Both types of bronchiectasis	3	7.0	120*	42.6	128*	46.2
Total specimens with endobronchial tuberculosis	12	27.9	98	34.8	133	48.0
Total specimens in group	43		282		277	

* and †. See table 3.

The specimens from patients who had moderate and far advanced disease were compared with those from patients with minimal disease.

TABLE 9

A Comparison of the Extent of Pulmonary Resection with the Type of Bronchial Disease in the Specimen

	WEDGE		SEGMENT		LOBECTOMY		LOBECTOMY PLUS WEDGE OR SEGMENT		PNEUMONECTOMY	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Bronchi normal	4†	36.4	26	12.7	21	11.1	3†	4.1	3*	2.4
Chronic bronchitis	4	36.4	87	42.4	45	23.8	17	23.0	20	16.3
Tuberculous bronchitis	2	18.2	34	16.6	41	21.7	9	12.2	35†	28.5
Bronchiectasis without endobronchial tuberculosis	0	0.0	37	18.0	42	22.2	27	36.5	23	18.7
Bronchiectasis with endobronchial tuberculosis	1	9.1	21	10.2	40*	21.2	18*	24.3	42*	34.1
Both types of bronchiectasis	1	9.1	58	28.3	82†	43.4	45*	60.8	65*	52.8
Total specimens with endobronchial tuberculosis	3	27.3	55	26.8	81*	42.9	27	36.5	77*	62.6
Total specimens in group	11		205		189		74		123	

* and †. See table 3.

The group of specimens removed by segmental resection was taken as the standard, and the groups of specimens removed by other types of resection were compared with it.

Influence of antimicrobial therapy: The present study was made during a period when therapeutic regimens were being altered frequently. The material does not lend itself, therefore, to a critical analysis of the effect of therapy upon

the tuberculous process. It did seem appropriate, however, to analyze the material in this connection in so far as combined streptomycin-PAS therapy might have any effect upon bronchial disease.

Three hundred and eleven of the specimens were resected from patients who had received four months or more of combined streptomycin-PAS therapy. In most cases, streptomycin, 1 gm. twice weekly, and PAS, 12 gm. daily, were given without interruption. Of this group, 161 had received the drugs for four through eight months, 87 for nine through twelve months, and 63 for thirteen months or longer. There were no appreciable differences in the incidence of the bronchial diseases in these groups.

TABLE 10

A Comparison of Preoperative Bronchoscopic Findings with the Type of Bronchial Disease in 582 Specimens

	NORMAL		RED OR FRIABLE MUCOSA		TUBERCULOUS BRONCHITIS		STENOSIS	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Bronchi normal	44	9.9	2	4.3	1	3.0	4	9.7
Chronic bronchitis	141	30.5	11	23.9	8	24.2	8	19.5
Tuberculous bronchitis	92	19.9	12	26.1	5	15.1	8	19.5
Bronchiectasis without endobronchial tuberculosis	102	22.1	10	21.7	5	15.1	9	21.9
Bronchiectasis with endobronchial tuberculosis	83	18.0	11	23.9	14*	42.4	12	29.3
Both types of bronchiectasis	185	40.1	21	45.6	19	57.5	21	51.2
Total specimens with endobronchial tuberculosis	175	37.9	23	50.0	19	57.5	20	48.8
Total specimens in group	462		46		33		41	

* Statistically significant at the 1 per cent level.

The group of specimens removed from patients with normal bronchoscopic findings was taken as the standard. The groups of specimens removed from patients with bronchoscopic abnormalities were compared with the standard.

In contrast, 173 specimens were resected from patients who had never received streptomycin-PAS, although many of these patients had been given short courses of streptomycin alone, PAS alone, or, in a few instances, isoniazid alone. However, 118 specimens were obtained from patients who had received streptomycin-PAS for one to four months. There was no significant difference in the incidence of bronchial abnormalities in these two groups.

The incidence of tuberculous bronchitis, bronchiectasis with endobronchial tuberculosis, and total specimens with endobronchial tuberculosis was significantly reduced in 311 specimens obtained from patients who had been treated for four or more months with streptomycin-PAS as compared to the 291 specimens from patients who had received lesser amounts of the drugs (table 11). Although such a reduction did occur, it is interesting to note that 32 per cent of the 311 specimens still had endobronchial tuberculosis. The incidence of bronchiectasis, nevertheless, was quite similar in both categories.

One hundred and fifty specimens were resected from 5 patients with minimal, 70 with moderately advanced, and 75 with far advanced, disease who had been treated for nine or more months with streptomycin-PAS. Of these specimens, 31 per cent had endobronchial tuberculosis and 45 per cent had bronchiectasis. When the 34 specimens with gross cavitation were removed from this group, the remaining 116 specimens showed a 23 per cent incidence of endobronchial tuberculosis. When 46 specimens containing liquefying lesions were removed from the 116 noncavitary specimens, the incidence of endobronchial tuberculosis dropped to 19 per cent. If all specimens which had ever shown roentgenographic evidence of cavitation were removed from the group of 70 specimens without cavitation or liquefying lesions, the incidence of endobronchial tubercu-

TABLE 11

A Comparison of the Duration of Preoperative Streptomycin-PAS Therapy with the Type of Bronchial Disease in the Specimens

	No therapy or streptomycin-PAS for less than four months		Streptomycin-PAS for four or more months	
	Number	Per Cent	Number	Per Cent
Bronchi normal	29	10.7	28	9.0
Chronic bronchitis	70	24.0	103	33.1
Tuberculous bronchitis	72	24.7	49†	15.7
Bronchiectasis without endobronchial tuberculosis	48	17.7	81	26.0
Bronchiectasis with endobronchial tuberculosis	72	24.7	50†	16.0
Both types of bronchiectasis	120	42.4	131	42.0
Total specimens with endobronchial tuberculosis	144	49.4	99*	31.7
Total specimens in group	291		311	

* and †. See table 3.

losis decreased further to 12 per cent. When cavitary specimens as well as specimens from far advanced cases and from patients who had had roentgenographic signs of cavitation were subtracted from the original group of 150, the incidence of endobronchial lesions in the remaining 44 specimens was still 27 per cent.

Bronchograms: Bronchograms were done on 80 patients from whom specimens were obtained. Bronchiectasis was found on 62 of the bronchograms; however, the bronchiectasis was confirmed only in 37 (60 per cent) of the specimens. Of the other 25 specimens, 16 showed chronic bronchitis and 6, tuberculous bronchitis. Five of the 18 specimens which came from patients with negative bronchograms actually had bronchiectasis in the specimen, and 7 of the 18 had endobronchial tuberculosis.

DISCUSSION

The histopathology of endobronchial tuberculosis in this series was similar to that described by Auerbach and others (7, 22, 33, 38, 39); however, the relatively less severe types of endobronchial disease predominated. In the

majority of instances, the lesions were composed principally of small submucosal tubercles.

Although the 40 per cent incidence of endobronchial tuberculosis and 42 per cent incidence of bronchiectasis are of considerable magnitude and importance, the figures are generally lower than those previously reported (5, 15, 24, 29, 34, 35–37, 40). The lower incidence in these surgical specimens primarily can be attributed to three factors: A large number of the specimens were resected from patients with minimal and moderately advanced disease; many of the patients had received streptomycin-PAS for prolonged periods; a majority of the specimens were noncavitary.

In this series, endobronchial lesions were frequently associated with "cellular" and open cavitary parenchymal foci, which were interpreted as signs of active tuberculous disease. They were also common in specimens from patients with more advanced tuberculosis of relatively recent origin. Since pulmonary tuberculosis is essentially a similar process in all age groups, and since interstitial fibrosis is not indicative of the activity of nodular or cavitary foci, these two factors of age and fibrosis were not expected to, nor did they, have an influence on the incidence of endobronchial tuberculosis. Furthermore, since chemotherapy is most beneficial in promoting the healing of superficial lesions such as those in the larynx, bronchi, gastrointestinal tract, and sinuses (41–44), a greater prevalence of endobronchial disease was anticipated and found in specimens from patients who had received little or no chemotherapy.

Bronchiectasis was most frequent in the specimens with fibrocaseous foci with much histopathologic evidence of healing and in specimens from patients with long-standing disease. This confirms the work of Jones and associates (24). Specimens from patients with more advanced or cavitary disease who required resection of one or more lobes were more likely to show bronchiectasis. Although larger amounts of streptomycin-PAS therapy significantly reduced the incidence of endobronchial tuberculosis associated with bronchiectasis, the prevalence of ectatic changes was not affected.

It should be emphasized that 37 per cent of the specimens from patients who had normal bronchoscopic examinations actually showed endobronchial lesions. In some instances these lesions were in the submucosa of the main stem bronchi. Similar findings have been reported by others (5, 22, 29). As might be expected, there was no important statistical correlation between bronchoscopic findings and the presence or absence of bronchiectasis. Nevertheless, when bronchoscopic abnormalities were found, there was a tendency for the percentage of both bronchiectasis and endobronchial lesions to increase.

The discrepancy between bronchograms and the actual specimens is not astonishing as similar findings have been reported by Buckles and associates (22). In those cases which were positive bronchographically for ectatic changes but negative to pathologic examination, the explanation may be the filling of small cavities and the misinterpretation of distortion produced by bronchitis. Moreover, it is probable that careful pathologic examination of the lung may uncover lesser degrees of bronchiectasis in all cases.

When the discrepancy is reversed and the specimens have definite ectatic

changes but the bronchograms are negative, the explanation may be incomplete bronchographic visualization of the finer bronchial branches of some upper lobe segments. Emphasis should be placed on the necessity of utilizing both techniques in order to obtain the closest possible correlation.

There was little evidence to indicate that endobronchial tuberculosis was the result of a hematogenous infection. Because of the infrequent involvement of the adventitia, the lymphatic nodules adjacent to the bronchial walls, and the hilar lymph nodes, it was concluded that lymphatic extension was seldom responsible for endobronchial lesions. As others have indicated, it seemed quite clear that the majority of endobronchial tuberculosis resulted from intrabronchial dissemination and implantation of bacilli in the mucosa (3, 5, 33, 34, 40). Without doubt the principal sources of the organisms were the cavities, inspissated cavities, and apparently "solid" nodules which in some cases had bronchial communications (14, 18, 28, 29, 33, 34, 37, 40, 45–48). Ample evidence has been presented that these parenchymal foci may contain significant numbers of bacilli (47, 49) which can be extruded into the bronchial lumen.

Although it was not the purpose of the present investigation to elucidate the pathogenesis of bronchiectasis in tuberculosis, a few comments in this connection may be offered. The present writers are in accord with others who have reported that, in addition to factors which contribute to improper drainage of the bronchi, infection is a major component in the pathogenesis of the disease (21, 50, 51). Destruction of the bronchial wall, following in the wake of the infection, plus the accumulation of secretions and necrotic debris within the lumen probably lead to the dilatation. As the acute destructive processes are slowly repaired with collagenous fibrous tissue, a permanently distorted and ectatic bronchus results. It is possible that the original infection may have been either an endobronchial tuberculosis or a nonspecific bronchitis. In those cases in which the original bronchitis is nonspecific, it would still be possible for secondary endobronchial tuberculosis to be superimposed on the ectatic bronchi by mechanisms similar to those which occur in the pathogenesis of simple tuberculous bronchitis.

SUMMARY

Six hundred and two surgical specimens resected from patients with pulmonary tuberculosis have been studied with particular reference to their bronchial pathology.

In only 10 per cent of the specimens were the bronchi normal. The incidence of different types of bronchial involvement was as follows: chronic bronchitis, 29 per cent; tuberculous bronchitis, 20 per cent; bronchiectasis without endobronchial tuberculosis, 21 per cent; and bronchiectasis with endobronchial tuberculosis, 20 per cent. Some degree of endobronchial tuberculosis was present in 40 per cent, and ectatic bronchi in 42 per cent, of the total specimens.

Of those specimens with bronchiectasis, 49 per cent had associated tuberculous endobronchial lesions. Hilar bronchial stenosis was present in 38 specimens. Thirty-three of 302 specimens had microscopic evidence of hilar endobronchial tuberculosis.

Tuberculous endobronchial foci were more frequently associated with "cellu-

lar" and open cavitary parenchymal foci. They were also more common in specimens from those patients who had moderate or far advanced disease, disease of less than three years' known duration, no streptomycin-PAS or less than four months of streptomycin-PAS, and lobectomies or pneumonectomies.

Bronchiectasis was more frequently associated with fibrocaseous parenchymal foci and moderate to marked interstitial pulmonary fibrosis. It was also more common in specimens from patients who had moderate or far advanced disease, disease of more than three years' known duration, and lobectomies or pneumonectomies. The duration of streptomycin-PAS therapy had no influence on the incidence of ectatic bronchi.

Noncavitary specimens from patients who had never had roentgenographic signs of cavitation and who had received nine or more months of streptomycin–para-aminosalicylic acid (PAS) still had a 27 per cent incidence of endobronchial tuberculosis.

The discrepancies between bronchoscopic findings and specimen histopathology have been indicated.

Explanations for the disparity between results of bronchographic and pathologic studies have been presented.

SUMARIO

Broncopatía en los Pulmones Resecados por Tuberculosis Pulmonar

Seiscientos y dos ejemplares quirúrgicos resecados de enfermos que tenían tuberculosis pulmonar han sido estudiados con referencia particular a su histopatología bronquial.

Sólo en 10 por ciento de los ejemplares eran normales los bronquios. La incidencia de las diversas formas de afección bronquial fué la siguiente: (1) bronquitis crónica, 29 por ciento, (2) bronquitis tuberculosa, 20 por ciento; (3) bronquiectasia sin tuberculosis bronquial, 21 por ciento, y (4) bronquiectasia con tuberculosis endobronquial, 20 por ciento. Había alguna tuberculosis bronquial en 40 por ciento y bronquiectasia en 42 por ciento del total de ejemplares. De los ejemplares bronquiectáticos, 49 por ciento tenían además lesiones tuberculosas endobronquiales. En 38 ejemplares existía estenosis broncohiliar. Treinta y tres de 302 ejemplares mostraban signos microscópicos de tuberculosis endobroncohiliar.

Los focos tuberculosos endobronquiales se asociaban más a menudo con focos parenquimatosos "celulares" y cavitarios abiertos. También abundaban más en los ejemplares procedentes de enfermos que tenían: (1) enfermedad moderada o muy avanzada; (2) enfermedad de menos de tres años de duración conocida; (3) menos de cuatro meses de tratamiento con estreptomicina-ácido para-aminosalicílico o no habían recibido tratamiento con esas drogas; y (4) lobectomías o neumonectomías en sus antecedentes. La duración de la terapéutica con estreptomicina-PAS no afectó en nada la incidencia de la bronquiectasia.

Los ejemplares no cavitarios procedentes de enfermos que jamás habían revelado signos radiográficos de cavernas y que habían recibido nueve o más meses de estreptomicina-PAS todavía mostraban una incidencia de 27 por ciento de tuberculosis endobronquial.

Apúntanse las discrepancias entre los hallazgos broncoscópicos y la histopatología de los ejemplares.

Ofrécense además explicaciones del desacuerdo entre los resultados arrojados por los estudios broncográficos y los histopatológicos.

RESUME

La lésion bronchique dans les poumons réséqués pour tuberculose pulmonaire

Six cent deux pièces, provenant de résections chirurgicales pratiquées chez des malades

atteints de tuberculose pulmonaire, ont été étudiées du point de vue particulier des signes de pathologie bronchique.

Dix pour cent seulement des spécimens ont montré des bronches normales. L'incidence des divers types de lésions bronchiques se répartissait comme suit: (1) bronchite chronique, 29%; (2) bronchite tuberculeuse, 20%; (3) bronchiectasie, sans tuberculose endobronchique, 21%; 4) bronchiectasie avec tuberculose endobronchique, 20%. Un certain degré de tuberculose endobronchique était présent dans 40% et l'ectasie bronchique était présente dans 42% de la totalité des spécimens. Parmi les spécimens avec bronchiectasie, 49% présentaient des lésions endobronchiques tuberculeuses associées. La sténose bronchique hilaire était présente dans 38 spécimens. Trente trois spécimens sur 302 présentaient des signes histologiques de tuberculose endobronchique hilaire.

Les foyers endobronchiques tuberculeux étaient plus fréquemment associés aux foyers parenchymateux cavitaires ouverts et "cellulaires". Ils étaient également plus fréquents dans les spécimens provenant des cas suivants: (1) affection modérée ou très avancée; (2) affection dont la durée reconnue était inférieure à trois ans; (3) aucun traitement streptomycine-PAS ou un traitement streptomycine-PAS d'une durée inférieure à quatre mois; (4) lobectomies ou pneumonectomies. La durée du traitement streptomycine- PAS n'influençait pas l'incidence de l'ectasie bronchique. Des spécimens non cavitaires prélevés sur des malades n'ayant jamais eu de signes radiologiques de lésions cavitaires et qui avaient été traités par la streptomycine-PAS pendant neuf mois, ou plus, présentaient néanmoins des lésions tuberculeuses endobronchique dont l'incidence était de 27%. Les divergences entre les résultats de l'examen bronchoscopique et l'histo-pathologie des spécimens ont été exposées. Les auteurs présentent des explications sur la disparité entre les résultats des études bronchographiques et histo-pathologiques.

Acknowledgment

The authors are particularly indebted to Mr. John Mullen for his invaluable assistance in the preparation of the microscopic tissue sections.

REFERENCES

(1) Birkelo, C. C., and Poznak, L. A.: Radiologic findings in tracheobronchial tuberculosis, Dis. of Chest, 1945, *11*, 26.

(2) Lorenz, T. H.: Bronchiectasis: A study of 220 proved cases, Am. J. M. Sc., 1951, *221*, 522.

(3) Ornstein, G. G., and Epstein, I. G.: Tuberculosis of major bronchi with little or no manifest pulmonary tuberculosis, Quart. Bull., Sea View Hosp., 1938, *3*, 109.

(4) Salkin, D., Cadden, A. V., and Edson, R. C.: Natural history of tuberculous tracheobronchitis, Am. Rev. Tuberc., 1943, *47*, 351.

(5) Sweany, H. C., and Behm, H.: Tuberculosis of trachea and major bronchi, Dis. of Chest, 1948, *14*, 1.

(6) Wilson, N. J.: Bronchoscopic observations in tuberculous tracheobronchitis: Clinical and pathological correlation, Dis. of Chest, 1945, *11*, 36.

(7) Aufses, A. H.: Tuberculous endobronchitis and upper lobe bronchiectasis, J. Thoracic Surg., 1943, *12*, 285.

(8) Barnwell, J. B., Litig, J., and Culp, J. E.: Ulcerative tuberculous tracheobronchitis, Am. Rev. Tuberc., 1937, *36*, 8.

(9) Dormer, B. A., Friedlander, J., and Wiles, F. J.: Bronchography in pulmonary tuberculosis: Normal or questionable roentgenographic findings in lungs and positive sputum, Am. Rev. Tuberc., 1944, *50*, 283.

(10) Dormer, B. A., Friedlander, J., and Wiles, F. J.: Bronchography in pulmonary tuberculosis: Radiographic black-out; evaluation of underlying lesions, Am. Rev. Tuberc., 1944, *50*, 287.

(11) Dormer, B. A., Friedlander, J., and Wiles, F. J.: Bronchography in pulmonary

tuberculosis: Chronic fibroid phthisis; chronic productive tuberculosis, Am. Rev. Tuberc., 1945, *51*, 62.

(12) Dormer, B. A., Friedlander, J., and Wiles, F. J.: Bronchography in pulmonary tuberculosis: Geographical adventure, Am. Rev. Tuberc., 1945, *51*, 455.

(13) Jones, E. M., Peck, W. M., and Willis, H. S.: Bronchiectasis following primary tuberculosis, Am. J. Dis. Child., 1946, *72*, 296.

(14) Auerbach, O.: The pathology of inflammatory diseases of the bronchi, Quart. Bull., Sea View Hosp., 1938, *3*, 134.

(15) Buckles, M. G., and Neptune, W. B.: Tuberculous bronchitis in pulmonary resection: Incidence in 58 pulmonary resections for tuberculosis, Am. Rev. Tuberc., 1950, *61*, 185.

(16) Meissner, W. A., Overholt, R. H., Wilson, N. J., and Walker, J. H.: The resected post-thoracoplasty lung: Clinico-pathologic correlation, Am. Rev. Tuberc., 1949, *60*, 406.

(17) Rafferty, T. N., and Shields, D. O.: Management of pulmonary tuberculosis, complicated by bronchial tuberculosis: With special reference to the use of artificial pneumothorax, J. Thoracic Surg., 1943, *12*, 225.

(18) Reichle, H. S., and Frost, T. T.: Tuberculosis of major bronchi, Am. J. Path., 1934, *10*, 651.

(19) Tuttle, W. M., O'Brien, E. J., Day, J. C., and Phillips, F. J.: Tuberculous stenosis of the major bronchi, J. Thoracic Surg., 1942, *11*, 299.

(20) Mendenhall, J. T.: Personal communication.

(21) Roberts, J. C., and Blair, L. G.: Bronchiectasis in primary tuberculous lesions associated with segmental collapse, Lancet, 1950, *1*, 386.

(22) Buckles, M. G., Potts, W. L., Davidson, N. B., and Neptune, W. B.: Bronchography in pulmonary tuberculosis with histopathologic correlation in 82 resections, Am. Rev. Tuberc., 1951, *64*, 394.

(23) Rabinowitz, P., and Harper, I. S. H.: Bronchography in pulmonary tuberculosis, Dis. of Chest, 1951, *19*, 66.

(24) Jones, E. M., Peck, W. M., Woodruff, C. E., and Willis, H. S.: Relationships between tuberculosis and bronchiectasis, Am. Rev. Tuberc., 1950, *61*, 387.

(25) Mitchell, E. B., and Thornton, T. F., Jr.: Lower lobe bronchiectasis associated with tuberculosis, Am. Rev. Tuberc., 1944, *49*, 38.

(26) Gordon, J., Brook, R., and Pratt, P. C.: Comparative study of tuberculous and nontuberculous pyogenic suppurative disease, J. Thoracic Surg., 1951, *22*, 411.

(27) MacRae, D. M., Hiltz, J. E., and Quinlan, J. J.: Bronchoscopy in a sanatorium: Review of 522 consecutive bronchoscopies, Am. Rev. Tuberc., 1950, *61*, 355.

(28) Myerson, M. C.: Tuberculosis of the trachea and bronchus, J. A. M. A., 1941, *116*, 1611.

(29) Overholt, R. H., and Wilson, N. J.: Pulmonary resection in treatment of pulmonary tuberculosis, Am. Rev. Tuberc., 1945, *51*, 18.

(30) British Tuberculosis Association Research Committee: Tuberculous tracheobronchitis, Tubercle, 1953, *34*, 74.

(31) Bickford, B. J., Edwards, F. R., Esplen, R., Jr., Gifford, J. H., Mair, A. M., and Thomas, O. F.: Lung resection for pulmonary tuberculosis, Thorax, 1951, *6*, 25.

(32) Stern, S. H., and Ehrenreich, T.: Pathology of excised tuberculous pulmonary specimens: Review of 127 specimens resected for pulmonary tuberculosis, Quart. Bull., Sea View Hosp., 1950, *11*, 149.

(33) Auerbach, O.: Tuberculosis of the trachea and major bronchi, Am. Rev. Tuberc., 1949, *60*, 604.

(34) Bugher, J. C., Littig, J., and Culp, J.: Tuberculous tracheobronchitis: Its pathogenesis, Am. J. M. Sc., 1937, *193*, 515.

(35) Silverman, G.: Tuberculosis of the trachea and major bronchi, Dis. of Chest, 1945, *11*, 3.

(36) Wilber, G. H.: Tuberculosis of the trachea and major bronchi, Quart. Bull., Sea View Hosp., 1942, *7*, 361.

(37) Meissner, W. A.: Surgical pathology of endobronchial tuberculosis, Dis. of Chest, 1945, *11*, 18.

(38) Auerbach, O.: The pathology of inflammatory diseases of the bronchi, Quart. Bull., Sea View Hosp., 1938, *3*, 134.

(39) Epstein, H. H., and Ornstein, G. G.: Tuberculosis of the trachea and main bronchi, Quart. Bull., Sea View Hosp., 1936, *1*, 273.

(40) Huang, C.: Tuberculous tracheobronchitis: Pathological study, Am. Rev. Tuberc., 1943, *47*, 500.

(41) Auerbach, O.: Anatomic changes in tuberculosis following streptomycin therapy, Tr. Sixth Conference on Chemotherapy of Tuberculosis, Veterans Administration, October, 1948, p. 251.

(42) Auerbach, O., Weiss, L., and Stemmermann, G. N.: Review of pathology in 34 autopsy cases of tuberculosis treated with streptomycin, Tr. Ninth Conference on Chemotherapy of Tuberculosis, Veterans Administration, 1950, p. 218.

(43) Council on Pharmacy and Chemistry: Streptomycin in the treatment of tuberculosis: Current status, J. A. M. A., 1948, *138*, 584.

(44) Olsen, A. M., and Hinshaw, H. C.: Tuberculosis of the trachea and major bronchi: Results of treatment with streptomycin, Am. Rev. Tuberc., 1949, *60*, 32.

(45) Auerbach, O., and Green, H.: The pathology of clinically healed tuberculous cavities, Am. Rev. Tuberc., 1940, *42*, 707.

(46) Auerbach, O., Katz, H. L., and Small, M. J.: The effect of streptomycin on the bronchocavitary junction and its relation to cavity healing and closure, Tr. Eleventh Conference on Chemotherapy of Tuberculosis, Veterans Administration, January, 1952, p. 219.

(47) Medlar, E. M.: Basic pathologic concepts, Nat. Tuberc. A. Tr., 1951, p. 245.

(48) Macleod, W. M., and Smith, A. T.: Some observations on the historical appreciation, pathological development, and behavior of round tuberculous foci, Thorax, 1952, *7*, 334.

(49) Ryan, B. J., Medlar, E. M., and Welles, E. S.: Simple excision in the treatment of pulmonary tuberculosis, J. Thoracic Surg., 1952, *23*, 327.

(50) Cohen, S. S., and Higgins, G. K.: Bronchiectasis associated with tuberculous bronchial obstruction, Am. Rev. Tuberc., 1937, *36*, 711.

(51) Lisa, J. R., and Rosenblatt, M. B.: Bronchiectasis, Oxford University Press, New York, 1943.

TUBERCULIN SENSITIVITY AND CONTACT WITH TUBERCULOSIS[1,2]

Further Evidence of Nonspecific Sensitivity

CARROLL E. PALMER

(Received for publication May 19, 1953)

INTRODUCTION

The time has come, it is apparent, for wider consideration of the proposition that tuberculin sensitivity in human beings is very often not due to tuberculous infection. The veterinarians have identified the so-called "no-lesion reactor" in cattle—tuberculin-sensitive animals that have no sign of tuberculosis on autopsy; and study of the problem has shown that tuberculin sensitivity may be caused by infection with nonpathogenic organisms as well as with virulent tubercle bacilli. It now appears that there may be, at least in some localities, a human counterpart of the no-lesion reactor in cattle.

The present paper deals with this problem, the specificity of tuberculin sensitivity in human populations. It illustrates how epidemiologic-statistical evidence leads directly to the conclusion that most of the sensitivity brought out only by strong doses of tuberculin is not caused by tuberculous infection, at least not by the same organism or by the same mode of infection responsible for tuberculous disease in human beings. This conclusion, supported by the findings of several previous studies (1), challenges the traditional assumption that all tuberculin sensitivity is necessarily of tuberculous origin and postulates the existence of at least two main sources of tuberculin sensitivity in human beings.

MATERIAL AND METHODS

Material for the present report is derived from a long-range cooperative tuberculosis research program begun ten years ago by the Public Health Service. Starting with the students in a small number of nurses' training schools in different parts of the country, the program was extended to include all, or nearly all, of the training schools in the metropolitan areas of Baltimore, Columbus (Ohio), Denver, Detroit, Kansas City, Los Angeles, Minneapolis, New Orleans, Philadelphia, and San Francisco. Details of the organization, scope, and methods of the work are given in previous papers (1 *b–d*). Material for the present paper includes tuberculin test results, inquiries about previous contact with tuberculosis, and all places of residence since birth.

The study population comprises almost all of the more than 22,000 new students admitted to 76 schools of nursing included in the program between 1943 and 1949. Most of the students (approximately 90 per cent) were 17 to 24 years

[1] From the Field Research Branch, Division of Chronic Disease and Tuberculosis, Public Health Service, Department of Health, Education, and Welfare.

[2] This is the seventh of a series of papers from a study of tuberculosis in student nurses, aided by a grant from the Committee on Medical Research of the American Trudeau Society, medical section of the National Tuberculosis Association.

of age; all were white women. The material used in the study consists of all but a small fraction of the total study population. The few persons who were missed were either not available for the testing or adamantly refused; or, for some reason, had a technically unsatisfactory test; or did not fill out the questionnaire. Fifty-two have been excluded because they had been previously BCG-vaccinated.

Tuberculin tests: Tuberculin tests were given and read in nearly all (21,313 of 22,170) of the total number of students admitted to training. Approximately 70 per cent were tested within the first two months of admission and 99 per cent within the first six months.

The tests were made with two dilutions of a single batch of tuberculin, PPD-S from the Henry Phipps Institute. The first dose of 0.0001 mg. (5 TU)[3] was given and read in 96 per cent of the students; the second dose of 0.005 mg. (250 TU) was given and read in 85 per cent of those reacting with less than 5 mm. of induration to the first dose.[4] Both tests were given in 0.1 ml. dilution, injected intradermally on the volar surface of the forearm; the transverse diameters of both erythema and induration were measured and recorded forty-eight hours later. Uniformity was obtained by having all of the work done by a special, trained Public Health Service team which periodically visited the cooperating schools; more than 95 per cent of all the tuberculin reactions were read by only two persons.

Contact with tuberculosis: Within a few months of entering the school of nursing, each student was asked to fill out a questionnaire, giving information about all contacts with persons who had tuberculosis: the kind of association she had had with each contact; the duration, frequency, and degree of contact (same room, same household, same school, et cetera); and the evidence that the person actually had tuberculosis (hospitalized for tuberculosis, died of tuberculosis, et cetera). This information covered history of contact up to the time of the first tuberculin test, given shortly after admission to training. The students had little opportunity to be exposed to patients with tuberculosis during the first few months of training, as their work consisted primarily of lectures, demonstrations, and classroom procedures.

The information recorded on the questionnaires depicted such a wide variety of kinds and degrees of contact that it was something of a problem to classify the students into groups representing different grades of exposure to infection. The first step was to sort all of the 22,000 questionnaires into approximately 35 categories, each representing a similar story of exposure. (This was done as an independent statistical operation without knowledge of the tuberculin test results or any other information which might have biased the classification.) At one extreme was a large group of students who reported that, so far as they could remember, they had never been associated with anyone thought to have tuberculosis; at the other extreme was a small group who had lived in intimate contact with one or more members of their own families who had died of tuberculosis. Those in between were graded, as well as could be judged, on a scale of increasing likelihood of having been infected, ranging from highly improbable to quite probable. For purposes of the present paper, adjacent categories were then

[3] One tuberculin unit (TU) is 0.00002 mg. (1/50,000 mg.) of PPD-S.

[4] Ten millimeters were used in the field as the criterion for giving the second-dose test, but for purposes of this paper the commonly accepted criterion of 5 mm. has been used.

combined to make three main groups, each containing a fairly large number of students:

1. *Close contact* included all students who had lived in the same household with one or more persons who probably had active pulmonary tuberculosis.
2. *Intermediate contact* included students who had been exposed outside the home (neighbor, boy friend, schoolmate, et cetera) or to a cured or arrested case of tuberculosis.
3. *No contact* included all students who reported they had never been exposed to tuberculosis.

FIG. 1. Division of the United States into ten geographical zones for classifying student nurses by place of residence.

A relatively small proportion, 3 per cent (approximately 600) of the students, were classified as having had close contact. Ten per cent were placed in the intermediate group, leaving a large proportion classified as having had no known contact.

This classification has obvious limitations. The three groups can hardly be regarded as representing anything more than rough approximations of degree and frequency of exposure. Yet the close-contact group should include many students who had been infected with tubercle bacilli during the first twenty years of their lives; some of them must have had fairly heavy infections; some must have been infected repeatedly. The no-contact group, on the other hand, should contain a much larger proportion of those who had completely escaped infection; it probably also contained more whose experience with tubercle bacilli could be described, if there is such a thing, as only a "light touch" kind of infection. It must be expected, however, that at least a few who reported no contact may unknowingly have had intimate contact with tuberculosis; and a few may have deliberately withheld information about contact.

Nevertheless, the groups can be expected to differ, and differ substantially, in two ways. The close-contact group should contain a higher proportion of in-

TABLE 1

DISTRIBUTION BY SIZE OF REACTION TO 0.0001 MG. OF PPD-S INTRADERMAL TUBERCULIN TEST

Student nurses tested and classified on admission to training by place of residence and history of contact with tuberculosis

TRANSVERSE DIAMETER OF INDURATION IN MM.	RESIDENCE CLASSIFICATION								
	Zone I-VII			Zone VIII-X			Mobile and Foreign		
	Contact			Contact			Contact		
	No	Intermediate	Close	No	Intermediate	Close	No	Intermediate	Close
0	10,579	1,001	199	1,179	106	13	4,006	438	119
1	21	2	—	5	1	—	5	—	1
2	315	33	5	31	2	—	132	11	3
3	110	6	1	30	3	—	51	5	1
4	72	3	2	27	5	1	25	8	2
5	76	7	1	34	3	—	38	6	6
6	44	3	1	14	—	—	22	3	1
7	47	10	5	15	—	—	35	3	2
8	30	8	3	6	1	—	15	1	3
9	14	1	1	3	—	1	6	1	2
10	136	22	14	21	9	3	89	21	13
11	39	9	3	5	2	—	29	2	2
12	77	14	10	9	1	1	50	14	8
13	48	9	4	8	1	1	16	2	1
14	30	7	5	6	—	—	18	4	3
15	151	30	19	12	3	2	95	16	8
16	52	15	9	7	—	1	28	3	5
17	62	14	9	5	1	—	25	7	4
18	49	16	5	4	—	—	29	7	5
19	16	3	5	2	—	—	15	6	2
20	148	38	22	14	1	1	73	20	9
21	34	5	—	2	—	—	15	2	2
22	53	12	5	4	3	—	27	5	4
23	21	6	6	2	1	—	13	3	3
24	12	1	4	1	—	—	7	1	2
25	42	5	3	—	2	—	27	6	2
26+	41	6	5	3	—	1	36	6	2
Previously positive*	27	5	5	—	—	—	3	2	1
Not testedor read†	442	60	21	74	10	1	175	22	9
Total	12,788	1,351	372	1,523	155	26	5,105	625	225

* Not tested on admission to training but known to be positive from earlier tests.
† Includes 52 students who received BCG prior to entrance.

fected students than the no-contact group, and among these there should be a higher proportion with heavy and repeated infections.

Place of residence: The student nurses probably represent, geographically, a fairly good sample of the young women of the United States. Some of the training schools were rather small and drew their students from the immediate sur-

TABLE 2

DISTRIBUTION BY SIZE OF REACTION TO 0.005 MG. PPD-S INTRADERMAL TUBERCULIN TEST

Student nurses (nonreactors to 0.0001 mg. of PPD-S) tested and classified on admission to training by place of residence and history of contact with tuberculosis

TRANSVERSE DIAMETER OF INDURATION IN MM.	RESIDENCE CLASSIFICATION								
	Zones I-VII			Zones VIII-X			Mobile and Foreign		
	Contact			Contact			Contact		
	No	Intermediate	Close	No	Intermediate	Close	No	Intermediate	Close
0	5,790	521	108	283	28	3	1,897	209	51
1	120	11	2	20	—	—	44	8	1
2	375	32	8	8	2	—	133	15	1
3	282	26	7	16	—	—	95	12	5
4	221	28	2	11	—	—	90	10	2
5	682	62	12	113	6	1	272	35	9
6	261	22	4	39	3	1	127	9	3
7	388	38	6	95	7	—	154	18	4
8	197	15	4	42	3	—	91	10	5
9	90	4	4	18	2	—	43	4	—
10	530	52	8	171	19	1	283	27	12
11	84	10	2	32	2	1	52	6	2
12	151	14	3	56	8	—	86	10	2
13	46	8	1	20	—	—	28	5	1
14	30	2	—	5	1	—	15	3	1
15	175	13	1	61	9	—	95	3	2
16	25	3	1	7	—	1	13	1	—
17	23	2	—	4	1	1	8	—	—
18	31	5	—	8	1	—	9	2	1
19	2	—	—	—	1	—	3	1	—
20	28	4	—	8	2	1	18	3	—
21	2	—	—	—	—	—	—	1	—
22	5	1	—	1	—	—	3	1	—
23	1	—	—	—	1	—	—	—	—
24	1	—	—	—	—	—	—	—	—
25	2	—	1	—	—	—	—	—	—
26+	—	1	—	—	—	—	—	—	—
Not tested or not read	1,555	171	33	254	21	4	660	69	24
Total	11,097	1,045	207	1,272	117	14	4,219	462	126

roundings, but some were large and so well known that students came from all over the country, occasionally even from abroad.

On entering school each student was asked to list in sequence, with dates, all the places where she had lived since birth. From this information they were classified according to residence. The United States was divided into ten zones, as shown in figure 1, and the student was considered a permanent resident of a particular zone if she had not been out of it for more than six months at any one time. Under this definition, more than 70 per cent of the total group could be classified

as permanent residents of some single zone in the United States. Nearly 10 per cent had lived outside the country or had had military service abroad; the remainder had lived in more than one zone within the country and were classified as *mobile-U.S.*

Tabulations: In tables 1 and 2 are given the tuberculin test results for the total study population, classified by degree of contact and grouped according to residence history into three main divisions. In table 1 may be seen the frequency distribution of the measured diameter of induration to the 0.0001 mg. (5 TU) test; in table 2, to the 0.005 mg. (250 TU) test.

RESULTS

Relation Between Contact and Sensitivity

In table 3 may be seen the results of the tuberculin tests for the students grouped according to degree of contact. The results are expressed, as is common practice, as the percentage of persons classified: (*1*) positive reactors to the first-dose (5 TU) tuberculin test, (*2*) positive reactors to the second-dose (250 TU) test, and (*3*) negative reactors to both tests. Reactions of less than 5 mm. of induration were defined as negative; those larger, as positive.

The top row of figures in table 3 shows how the frequency of first-dose reactors increased with the degree of contact with tuberculosis; 11.4 per cent of the students in the no-contact group were positive as compared with 20.4 per cent in the intermediate, and 41.4 per cent in the close-contact, groups. There is thus nearly a fourfold difference between the two extremes of contact. The next row of figures shows that the frequency of positive reactors to the second-dose test decreased with increased degree of contact, which is just the opposite of what was found with the first dose.

When the percentages of positive reactors to either dose were added together (next to bottom row in table 3), an increase in the proportion of reactors with increase in contact was again found, but the differences among the three groups were much less, in both absolute and relative terms, than were found for the first-dose reactors alone. Instead of a fourfold increase, the close-contact group was only one and one-half times that of the no-contact group—roughly, an increase from 40 to 60 per cent.

Although similar results have been obtained in other studies, their interpretation depends on whether it be assumed beforehand that all positive reactors, regardless of test dose, have been infected with tuberculosis. Suppose, for purposes of illustration, that assumption is made. First, the increase in frequency of infected students with increase in exposure to tuberculosis would be noted; approximately 40 per cent with no known contact and 60 per cent with close contact were positive reactors (to either dose). It would then be observed that, among the positives in the no-contact group, only one of 4 was highly sensitive (reacted to the first dose) compared with 4 of 6 with close contact. The lower proportion of highly sensitive persons in the no-contact group would undoubtedly be interpreted as meaning that, among the infected, relatively fewer were heavily or repeatedly infected. So far, the findings seem consistent with the assumption

that all tuberculin sensitivity signifies tuberculous infection and, further, that the degree of sensitivity is related to the degree of infection.

The same findings, however, may be shown to support the hypothesis that second-dose tuberculin sensitivity is *not* related to tuberculous infection. Pertinent evidence is found by asking whether second-dose reactions, taken independently, are related to contact with tuberculosis, as is clearly the case with first-dose reactions. To be eligible for the second-dose test, a student must have been negative to the first-dose test. The frequency of second-dose reactors should therefore be expressed as a percentage of those eligible to be second-dose reactors, i.e., as a percentage of those negative to the first dose, as given in the bottom row of figures in table 3.[5] Almost exactly the same proportion in each of the three

TABLE 3

PERCENTAGE OF REACTORS TO 0.0001 MG. (5 TU) AND 0.005 MG. (250 TU) INTRADERMAL TUBERCULIN TESTS IN STUDENT NURSES CLASSIFIED BY HISTORY OF CONTACT WITH TUBERCULOSIS

CLASSIFICATION OF REACTORS	NO CONTACT	INTERMEDIATE CONTACT	CLOSE CONTACT	TOTAL
Positive to 5 TU	11.4	20.4	41.4	13.1
Negative to 5 TU Positive to 250 TU	29.7	26.9	19.7	29.2
Negative to 250 TU	58.9	52.7	38.9	57.7
Total	100.0	100.0	100.0	100.0
Positive to either 5 TU or 250 TU	41.1	47.3	61.1	42.3
Positive to 250 TU among those negative to 5 TU	33.5	33.8	33.6	33.6

groups (34 per cent), or one of every 3 students, was positive to the second dose. The frequency of second-dose reactors did not increase with degree of contact, as did the frequency of first-dose reactors. In fact, the frequency of second-dose reactions varied just as they would be expected to vary if they had nothing whatever to do with tuberculosis.

How can these findings be interpreted as being consistent with the assumption that second-dose reactions are specific for tuberculous infection? It might be proposed that they represent a minimal degree of infection, so transmitted that everyone in the population has an equal chance of becoming infected, regardless of exposure to known sources of infection. The principal weakness of such a proposal, however, is the difficulty of explaining why there is no correlation between the frequency of heavy infections which arise from contact and the minimal kind not transmitted by contact. Conditions favoring many heavy or repeated infections should certainly favor many light ones, and vice versa.

[5] For example, in the close-contact group 19.7/(100 − 41.4) = 33.6 per cent.

Size of Tuberculin Reactions and Degree of Contact

Additional evidence concerning the nature of tuberculin sensitivity is revealed by comparing the sizes of the reactions in each of the three contact groups. If, in keeping with the classical concept, the intensity of sensitivity is determined by the degree of infection, larger reactions might be expected among the positives in the close-contact group, for this group undoubtedly contained more students who had been heavily and repeatedly infected than the no-contact group. The upper half of figure 2 shows the first-dose reactions distributed by size of induration for each degree of contact.

In their general form, the three histograms are much alike; in each, the reactions are concentrated in two parts of the scale. One large group, ordinarily designated as negative, fell below 5 mm. in size; the other, the positives, were concentrated in the range between 10 and 25 mm. Relatively few reactions appeared in the 5 to 9 mm. interval separating the two groups. The histograms clearly differed in the relative proportion of negative and positive reactions, as expected from the results in table 3: there were relatively many more positive reactions (and correspondingly fewer negative reactions) in students who reported close contact than in those with no contact, and the intermediate group stood midway between. Yet, despite the differences in proportion, the positive reactions in all of the three groups were distributed in a similar pattern and covered the same range on the size scale. The reactions in the close-contact group were not larger than those in the no-contact group. This is strikingly emphasized by the fact that the average size of reactions exceeding 9 mm. in diameter was almost exactly the same for all three groups: 16.5 mm., 16.6 mm., and 16.6 mm.

The effect of increasing degree of contact thus appears simply to increase the chances of becoming sensitive to the 5 TU test: some reactions are large, some small, their size evidently being related to a person's capacity to respond to the antigenic stimulus of infection, not to the degree or frequency of contact.

Histograms for the sizes of second-dose reactions are given in the lower half of figure 2. The percentages are based on the number of students who were negative to the first-dose test and were therefore given the second dose. The three histograms are so alike for the three degrees of contact as to be almost indistinguishable. All show sharply decreasing frequencies from the highest column on the left to the lowest on the right. Few reactions exceeded 14 mm. in diameter. Unlike the histograms for the first-dose test, where the reactions were concentrated in two quite clearly separated groups on the size scale, the second-dose distributions give no clue how to separate what might be called positive and negative reactions. A break at any point on the size scale is obviously arbitrary and not very meaningful. It is also clear from the figure that both the frequency and the size of second-dose reactions were entirely independent of degree of contact with tuberculosis.

Relation Between Place of Residence and Sensitivity

Another important fact about tuberculin sensitivity is found by taking the geographic place of residence into account, as shown in table 4. The 14,000 stu-

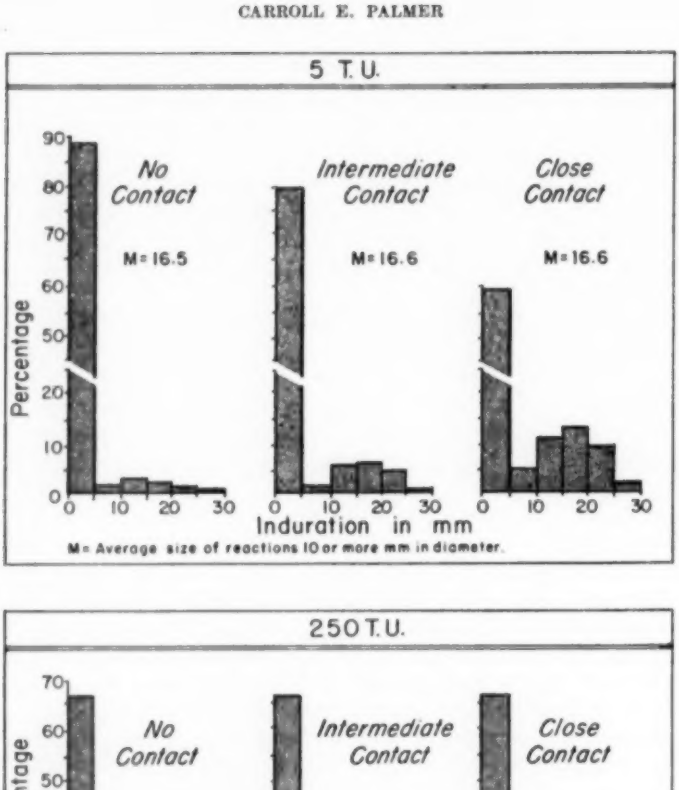


FIG. 2. Histograms of size of reactions to 0.0001 mg. (5 TU) and 0.005 mg. (250 TU) intradermal tuberculin tests in student nurses classified by history of contact with tuberculosis.

dents classified as permanent residents of zones I through VII have been put into one group; the 1,700 of zones VIII through X, in the other. (Students classified as *mobile-U.S.* and as military and foreign residents are not included here.) For each of the two geographic subdivisions and for each degree of contact, table 4*A* gives the percentage of students who had positive reactions to the first-dose test; and table 4*B* gives the percentage of students among those negative to the first dose who had positive reactions to the second-dose test.

The results in table 4*A* show very nearly the same frequency of positive reactors, approximately 12 to 13 per cent, to the 5 TU dose of tuberculin in both geographic areas. Furthermore, the two areas do not differ in the relation between degree of contact and first-dose sensitivity. Approximately 10 per cent of the no-contact, 20 per cent of the intermediate, and 40 per cent of the close-contact, groups were positive reactors.

In sharp contrast, the frequency of reactors to 250 TU (table 4*B*) varied with place of residence and had no relation to degree of contact. Less than 30 per cent of the students in zones I–VII but nearly 70 per cent from the southeastern

TABLE 4*A*

PERCENTAGE OF REACTORS TO 0.0001 MG. (5 TU) INTRADERMAL TUBERCULIN TEST IN STUDENT NURSES CLASSIFIED BY HISTORY OF CONTACT WITH TUBERCULOSIS AND PLACE OF RESIDENCE

PLACE OF RESIDENCE	NO CONTACT	INTERMEDIATE CONTACT	CLOSE CONTACT	ALL CONTACT GROUPS
Zones I–VII	10.1	19.1	41.0	11.7
Zones VIII–X	12.2	19.3	44.0	13.3
All zones	10.3	19.1	41.2	11.9

TABLE 4*B*

PERCENTAGE OF REACTORS TO 0.005 MG. (250 TU) INTRADERMAL TUBERCULIN TEST IN STUDENT NURSES (NONREACTORS TO 5 TU) CLASSIFIED BY HISTORY OF CONTACT WITH TUBERCULOSIS AND PLACE OF RESIDENCE

PLACE OF RESIDENCE	NO CONTACT	INTERMEDIATE CONTACT	CLOSE CONTACT	ALL CONTACT GROUPS
Zones I–VII	28.9	29.3	27.0	28.9
Zones VIII–X	66.8	68.8	70.0	67.0
All zones	32.5	33.2	29.3	32.5

states (zones VIII–X) were designated as positive to the second dose, regardless of whether they were classified as having had close, intermediate, or no contact with tuberculosis.

Together, tables 4*A* and 4*B* clarify one more point about tuberculin sensitivity. Both the frequency of first-dose reactors and the relation between degree of contact with tuberculosis and frequency of first-dose reactors is approximately the same in the two geographic subdivisions. But second-dose sensitivity is obviously associated with place of residence. Evidently there is, in the southeastern part of the United States, a source of sensitivity found primarily in that section of the country.

Size of Tuberculin Reactions and Place of Residence

Histograms for the first-dose tuberculin reactions of residents of the two geographic subdivisions are given in the upper section of figure 3. (Close and inter-

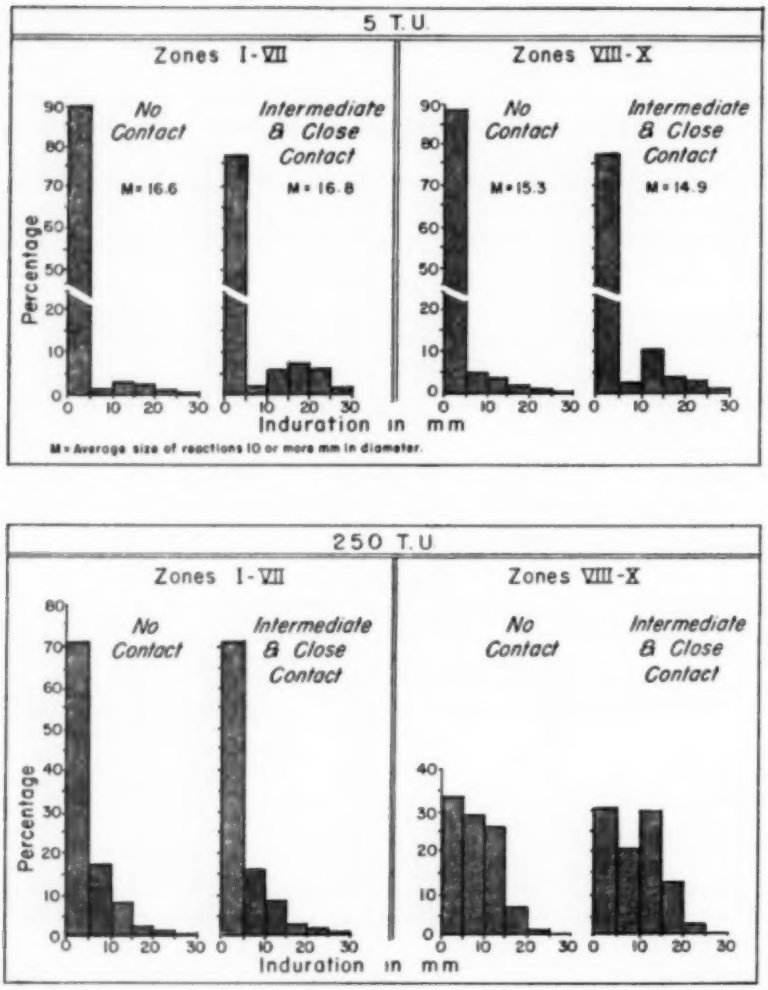


FIG. 3. Histograms of size of reactions to 0.0001 mg. (5 TU) and 0.005 mg. (250 TU) intradermal tuberculin tests in student nurses classified by history of contact with tuberculosis and place of residence.

mediate classes of contact have been combined because of rather small numbers in some of the subgroups.) While the average sizes of reactions classified as positive were not affected by degree of contact, as previously shown, they did seem to be slightly influenced by place of residence. Students from the southeastern part of the country (zones VIII through X) had somewhat smaller positive reactions than residents of zones I through VII. As indicated on the graphs, the

average size of reactions over 9 mm. was approximately 15 mm. for both contact groups in the southeast as compared with nearly 17 mm. for the rest of the country.

Histograms for the 250 TU reactions, in the lower section of figure 3, reveal significant differences between the two geographic areas in the pattern of second-dose reactions; again, these differences are not associated with the degree of contact. For zones I through VII, distributions representing both contact groups had the same high frequency of zero to 4 mm. reactions, followed by a precipitous steplike decrease of frequency in each successive reaction-size category. Relatively few reactions exceeded 9 mm.; very few exceeded 14 mm. In contrast, the distributions for zones VIII through X started with a much lower frequency of zero to 4 mm. reactions and bulged out to form a high plateau before a more gradual falling off above 14 mm. The strikingly higher frequency of moderate-to-large-sized reactions in the southeast is emphasized by the fact that approximately 40 per cent of the students had reactions exceeding 9 mm. in size, whereas in zones I through VII the corresponding frequency was only 12 per cent.

These results reveal several characteristics of the sensitivity brought out by a strong dose of tuberculin. First, as confirmed by more detailed analysis of the material, neither the frequency nor the degree of second-dose sensitivity is associated with exposure to tuberculosis. Persons living in the southeastern states are much more likely to react to the second-dose test, and they have larger reactions, than persons from the rest of the country. Finally, in the geographic areas where second-dose sensitivity is highly prevalent, the average size of positive first-dose reactions tends to be slightly reduced. Alone, this latter observation might seem unimportant; but the same finding has been reported in other studies (1 *e* and *g*) and has been interpreted as suggesting some kind of interaction between first- and second-dose sensitivity. Another possible explanation is that some persons with very strong second-dose sensitivity have small first-dose reactions. The effect of including them among the first-dose reactors would then be twofold: to increase slightly the frequency, and to decrease slightly the average size, of positive first-dose reactions.

DISCUSSION

The present paper adds critical evidence to support the view that naturally acquired tuberculin sensitivity in human beings can no longer be regarded as being derived from a single source. Such a proposition should not be surprising, for the labor of science is largely one of seeking and separating the component parts of what often first appears to be a single entity. A decade ago, for example, it was believed that pulmonary calcification was an almost unequivocal sign of pulmonary tuberculosis, yet it is known today that histoplasmosis, in certain geographic areas, accounts for as much as or more pulmonary calcification than tuberculosis.

With respect to tuberculin sensitivity the situation seems to be analogous. For many years tuberculin sensitivity has been believed to be an almost unequivocal sign of tuberculous infection. But, in putting together all of the evi-

dence now available, it becomes apparent that this belief holds good only for the high degree of sensitivity elicited by a weak dose of tuberculin, a dose close to 5 TU for the intradermal test. Specific sensitivity, so defined, is almost universally found in persons ill with tuberculosis (1 *f*) and in those with definite signs of having had the disease (1 *b* and *c*). It varies with the prevalence of tuberculosis, apparently corresponding with fluctuations in mortality from country to country, and from place to place within countries; and it is generally higher in urban than in rural areas. Defining specific sensitivity as only low-dose sensitivity is entirely consistent with the spread of tuberculosis by direct contact between persons with the disease and uninfected persons. Such low-dose sensitivity is very often found in apparently healthy persons who give a history of having been exposed; much less often in those without known exposure.

The sensitivity brought out only by strong doses of tuberculin might be called "nonspecific" in that it is apparently derived from a different (still unidentified) source. Not only is nonspecific sensitivity a much milder degree of allergy than the specific kind, it also differs in other characteristic ways. It is independent of known contact with tuberculosis; it is not correlated with either the prevalence of tuberculosis or specific sensitivity. This low-grade kind of sensitivity is clearly related to place of residence (1 *d*, *e*, and *g*). It is highly prevalent in some countries, apparently absent in others; it is much more prevalent in the southeastern part of this country than in the north and west. In addition, its frequency has been shown to vary in India with altitude of residence above sea level and to be higher in rural than in urban areas in the United States.

In order to reconcile a belief in the specificity of both weak- and strong-dose sensitivity, it would be necessary to explain how tuberculosis can be transmitted in two distinctly different and uncorrelated ways. The crux of the problem, apparently, is to explain how the same microorganism can, in the one instance, be transmitted by personal contact and produce first-dose sensitivity and, in the other, be transmitted in some different way and produce second-dose sensitivity.

A simpler and more likely explanation is that second-dose sensitivity is caused by a different organism than the ordinary human (or bovine) type of tubercle bacilli which produces first-dose sensitivity and tuberculous disease in human beings. The organism responsible for the nonspecific kind of sensitivity would be antigenically related to the tubercle bacillus—probably a variety of *Mycobacterium*. There is good reason to believe that it is not, as a rule, pathogenic for human beings, and a number of possibilities have already been suggested (2).

It is known that tuberculin sensitivity can be produced in experimental animals by a variety of acid-fast organisms, some pathogenic, some nonpathogenic. Extensive work in this field (for examples, (3 *a*, *b*, *c*, *d*)) has made it clear that experimentally infected animals usually have a higher degree of sensitivity to tuberculin prepared from the infecting organism, the homologous antigen, than to most of the heterologous antigens prepared from related organisms. By analogy, it can be reasoned that the kind of low-level sensitivity elicited by strong doses of human-type tuberculin in human beings may well represent a type of "cross-reaction," a sensitivity to a heterologous antigen. The agent re-

sponsible for producing this sensitivity might be found by testing human populations with tuberculins prepared from different kinds of *Mycobacteria*. Careful quantitative studies along such lines could lead to the identification of the homologous antigen, and so to the organism responsible for nonspecific sensitivity.

Unless evidence is found to reject the hypothesis of the nonspecific nature of second-dose sensitivity, it would certainly seem advisable, in tuberculin-testing work, to distinguish clearly between the results obtained with large and small doses of tuberculin. If, as seems most likely, intradermal tests with doses as large as 1 mg. of OT or 0.005 mg. of PPD bring out a kind of sensitivity which has nothing whatever to do with tuberculosis, many of the traditional views of tuberculosis may have to be revised. Combined frequencies of positive reactors to first- and second-dose tests (as recommended by Rich (4), for example) must give an unduly magnified and distorted picture of tuberculosis infection rates in many parts of this and other countries.

SUMMARY

More than 22,000 young women who entered seventy-six schools of nursing throughout the United States between 1943 and 1949 were tuberculin tested with two doses (0.0001 mg. and 0.005 mg.) of PPD and answered questionnaires on history of contact with tuberculosis and on all places of residence since birth.

Analysis of the material shows the frequency of first-dose reactors to increase, as expected, with increasing degree of contact with tuberculosis: from approximately 10 per cent positive in the group reporting no contact to 20 per cent in those with intermediate, and 40 per cent in those reporting close, contact. Yet, the average sizes of the reactions did not vary with degree of contact. Increased exposure simply affects the frequency, not the intensity, of first-dose sensitivity. Moreover, place of residence does not affect the relation between contact and first-dose sensitivity.

In contrast, the frequency of second-dose reactors, expressed as a percentage of those negative to the first-dose test, is shown to be entirely independent of degree of contact, but closely related to place of residence. Nearly 70 per cent of the permanent residents of the southeastern states were positive to the second dose, compared with less than 30 per cent in the rest of the country, regardless of whether they were classified as having had close, intermediate, or no contact with tuberculosis. Furthermore, 40 per cent of those from the southeast had reactions exceeding 9 mm. in diameter, compared with 12 per cent from the north and west.

The results of the present paper, together with previously published material, are consistent with the hypothesis that tuberculin sensitivity in human beings can no longer be regarded as being derived from a single source. Most reactions elicited by a low-dose intradermal test (approximately 0.0001 mg. of PPD) undoubtedly indicate specific infection with virulent tubercle bacilli, spread by personal contact. Low degrees of sensitivity brought out only by large doses (1 mg. of OT or 0.005 mg. of PPD, for example) apparently represent infection by a different organism with a different mode of transmission. The latter (un-

identified) organism must be antigenically related to the tubercle bacillus, highly prevalent in certain geographic areas, and apparently nonpathogenic for human beings.

SUMARIO

La Sensibilidad a la Tuberculina y el Contacto con la Tuberculosis: Nuevas Pruebas de Sensibilidad Anespecífica

Más de 22,000 mujeres jóvenes que ingresaron en 76 escuelas de enfermería de todas partes de los Estados Unidos entre 1943 y 1949 fueron comprobabdas tuberculínicamente con dos dosis (0.0001 mg. y 0.005 mg.) del derivado proteínico purificado (DPP) y contestaron cuestionarios en que se les pedían antecedentes de contacto con tuberculosis en todos los sitios donde habían residido desde el nacimiento.

El análisis de las contestaciones demuestra, como era de esperar, la frecuencia con que aumentan los reactores a la primera dosis mientras mayor es el contacto con la tuberculosis: desde 10 por ciento aproximadamente de positivos en el grupo que no menciona contacto alguno a 20 por ciento en las que mencionan contacto intermedio y 40 por ciento en las que mencionan contacto íntimo. Sin embargo, los tamaños medios de las reacciones no variaron de acuerdo con la intensidad del contacto. La mayor exposición afecta meramente la frecuencia, no la intensidad, de la sensibilidad a la primera dosis.

En contraposición, la frecuencia de los reactores a la segunda dosis, expresada en porcentaje de las negativas a la primera dosis, resultó ser absolutamente independiente de la intensidad del contacto, pero estaba íntimamente enlazada con el lugar de residencia. Cerca de 70 por ciento de las que residían permanentemente en los Estados del Sudeste del país fueron positivas a la segunda dosis, comparado con menos de 30 por ciento en el resto del país, prescindiendo de si el contacto con la tuberculosis había sido clasificado como íntimo, intermedio o nulo. Además, 40 por ciento de las del Sudeste tuvieron reacciones que excedían de 9 m.m. de diámetro, comparado con 12 por ciento en las del Norte y del Oeste.

Los resultados del trabajo actual, junto con estudios previamente publicados, son compatibles con la hipótesis de que no cabe ya considerar la sensibilidad a la tuberculina en los seres humanos como derivada de una sola causa. La mayor parte de las reacciones provocadas por una prueba intradérmica con una dosis baja (aproximadamente 0.0001 mg. de DPP) indican sin duda infección específica por bacilos tuberculosos virulentos, diseminados por el contacto personal. Los bajos tenores de sensibilidad exteriorizados únicamente por dosis grandes (1 mg. de TA o 0.005 mg. de DPP., por ejemplo) representan aparentemente infección por un microbio distinto que se transmite en otra forma. Ese último microbis (sin identificar) debe estar relacionado antigémicamente con el bacilo tuberculoso, ser sumamente frecuente en ciertas zonas geográficas y al parecer anapatógeno para el hombre.

RESUME

Sensibilité à la tuberculine et contact avec la tuberculose: Preuves nouvelles d'une sensibilité non-spécifique

Plus de 22.000 jeunes femmes admises dans les 76 écoles d'infirmières des Etats-Unis ont été soumises au tuberculine-test. Le dérivé protéique purifié PPD a été utilisé à la dose de 0,0001 mg. et de 0,005 mg. Les membres du groupe ont répondu à un questionnaire réclamant l'historique de leur contact avec la tuberculose et l'indication des lieux de séjour depuis la naissance.

L'analyse des documents montre que la fréquence des réactions de "première-dose" augmentait au fur et à mesure que s'accroissait le degré du contact avec la tuberculose—comme on pouvait s'y attendre—il y avait approximativement 10% réactions positives pour les membres du groupe déclarant l'absence d'un contact avec la tuberculose, 20% pour les

membres modérément exposés et 40% pour ceux déclarant qu'ils étaient en contact étroit avec la tuberculose. L'importance de la réaction n'a toutefois pas varié selon le degré de l'exposition à la tuberculose. L'augmentation du degré de l'exposition affectait simplement la fréquence et non l'intensité de la sensibilité à la "première-dose".

En contraste, la fréquence des réactions à la "deuxième-dose", exprimée par rapport aux réactions négatives au test de "première-dose" se montre absolument indépendante du degré de l'exposition à la tuberculose, mais étroitement liée au lieu de la résidence. Près de 70% des habitants permanents des états du Sud-Est présentaient une réaction positive à la "deuxième-dose", par comparaison avec moins de 30% obtenus pour le reste du pays; sans tenir compte des conditions d'exposition à la tuberculose (absence de contact, exposition modérée, contact étroit). De plus, 40% des sujets du Sud-Est présentaient une réaction dont les dimensions dépassaient 9 mm. de diamètre, par rapport aux 12% représentés par les sujets du Nord et de l'Ouest.

Les résultats exposés dans cet article, comme dans les publications antérieures, confirment l'hypothèse que, chez l'homme, la sensibilité à la tuberculine ne peut plus être attribuée à une source unique. La plupart des réactions élicitées par le test intradermique à dose faible (approximativement 0,0001 mg. de PPD) indiquent nettement la présence d'une infection spécifique par bacilles tuberculeux virulents et transmise par un contact personnel. Les degrés de sensibilité bas, qui ne se révèlent qu'avec l'emploi de doses fortes (par exemple 1 mg. de Vieille tuberculine (OT) ou 0,005 mg. de PPD) représentent probablement l'infection par un microorganisme différent et un mode de transmission différent. Cet organisme (non identifié) doit être, du point de vue antigène, apparenté au bacille tuberculeux, prédominant dans certaines régions géographiques et, selon les apparences, non pathogène pour l'homme.

Acknowledgment

The study of tuberculosis in student nurses, now in its tenth year, has needed and has had the help of many people. Most have helped briefly, a few from the beginning. Among the latter, the writer wishes especially to acknowledge at this time the patient and understanding support of four colleagues: Howard Bosworth of Los Angeles, David Cooper of Philadelphia, Herbert Mantz of Kansas City, and J. Arthur Myers of Minneapolis. The wide geographic coverage and the continuation of observations over a period of years would not have been possible without them.

The writer also wishes to thank Louise Hopwood and Sven Nissen Meyer for technical assistance on the present paper.

REFERENCES

(1) *a.* Furcolow, M. L., Hewell, B., Nelson, W. E., and Palmer, C. E.: Quantitative studies of the tuberculin reaction: I. Titration of tuberculin sensitivity and its relation to tuberculous infection, Pub. Health Rep., 1941, *56*, 1082.

b. Edwards, L. B., Lewis, I., and Palmer, C. E.: Studies of pulmonary findings and antigen sensitivity among student nurses: III. Pulmonary infiltrates and mediastinal adenopathy observed among student nurses at the beginning of training, Pub. Health Rep., 1948, *63*, 1569

c. Goddard, J. C., Edwards, L. B., and Palmer, C. E.: Studies of pulmonary findings and antigen sensitivity among student nurses: IV. Relationship of pulmonary calcifications with sensitivity to tuberculin and histoplasmin, Pub. Health Rep., 1949, *64*, 820.

d. Palmer, C. E., Ferebee, S. H., and Strange Petersen, O.: Studies of pulmonary findings and antigen sensitivity among student nurses: VI. Geographic differences in sensitivity to tuberculin as evidence of non-specific allergy, Pub. Health Rep., 1950, *65*, 1111.

e. Bates, L. E., Buse, T., and Palmer, C. E.: Research contributions of BCG vac-

cination programs: II. Tuberculin sensitivity at different altitudes of residence, Pub. Health Rep., 1951, *66*, 1427.

f. PALMER, C. E., AND BATES, L. E.: Tuberculin sensitivity of tuberculous patients, Bull. World Health Organization, 1952, *7*, 171.

g. EDWARDS, L. B., AND PALMER, C. E.: Geographic variation in naturally acquired tuberculin sensitivity, Lancet, 1953, *1*, 53.

(2) *a*. FENNER, F.: Studies on *Mycobacterium ulcerans:* II. Cross-reactivity in guinea-pigs sensitized with *Mycobacterium ulcerans* and other mycobacteria, Australian J. Exper. Biol. & M. Sc., 1952, *30*, 11.

b. LINELL, F., AND NORDEN, A.: Hudinfektioner i simhall genom ny art av Mycobacterium, Nord. med., 1952, *26*, 888.

c. PAYNE, R.: Personal communication.

(3) *a*. CRAWFORD, A. B.: Tuberculin sensitivity in guinea pigs caused by various acid-fast organisms, J. Am. Vet. M. A., 1926, *69*, 579.

b. PLUM, N.: Studies on tuberculosis and tuberculin reactions in cattle, Skandinav. Veterinaer Tidskrift, 1937, *27*, 589.

c. GREEN, H. H.: Weybridge P.P.D. tuberculins, Vet. J., 1946, *102*, 267.

d. TARSHIS, M. S., AND FRISCH, A. W.: Chromogenic acid-fast bacilli from human sources: III. Hypersensitivity studies, Am. Rev. Tubere., 1952, *65*, 302.

(4) RICH, A.: The Pathogenesis of Tuberculosis, Charles C Thomas, Springfield, Illinois, 1951, p. 213.

THE OCCURRENCE OF PULMONARY LESIONS IN BCG-VACCINATED AND UNVACCINATED PERSONS[1]

SAMUEL C. STEIN AND JOSEPH D. ARONSON

(Received for publication June 15, 1953)

INTRODUCTION

A joint investigation was undertaken by the Henry Phipps Institute, University of Pennsylvania, and the Branch of Health, Bureau of Indian Affairs, Department of the Interior, to appraise the specific immunizing value of BCG vaccine in the control of tuberculosis. Some evaluation of the specific protection of this vaccine against tuberculosis has been made previously (1, 2, 3, 4), based primarily on a comparison of tuberculosis mortality rates among the BCG-vaccinated group and the nonvaccinated controls. Further objective knowledge of the effect of BCG vaccine on the occurrence, evolution, and course of tuberculosis was to be found by comparing the morbidity from tuberculosis in the two groups on the basis of annual roentgenograms of the chest taken during the period of 1936 to 1947, inclusive.

The investigation was conducted in five different geographical areas of the United States. These were the Pima Agency, Arizona, inhabited by the Pima tribe; the Wind River Agency, Wyoming, inhabited by the Shoshone and the Arapaho tribes; the Turtle Mountain Agency, North Dakota, inhabited by Chippewas; the Rosebud Agency, South Dakota, inhabited by Sioux Indians; and twelve communities of southeastern Alaska, peopled by members of the Tlingit, Tsimshian, and Haida tribes.

The study was initiated at the Pima Agency, Arizona, in December, 1935. In 1936, it was extended to include the Shoshone and Arapaho tribes of the Wind River Agency, Wyoming, and the Chippewa Indians of the Turtle Mountain Agency, North Dakota. In 1937 and 1938, the Sioux Indians of the Rosebud Agency, South Dakota, and the Indians of southeastern Alaska were added to the study, as well as a second group at the Pima Agency, Arizona.

GENERAL PLAN OF INVESTIGATION

To select those who were tuberculin negative among the Indian population of the different areas, the tuberculin test was conducted on a total of 8,420 persons ranging in age from less than one year to sixty years and older. This group represented a cross-section of the population, including all children of school age.

An initial intracutaneous injection of 0.00002 mg. of purified protein derivative (PPD) tuberculin was made in the skin of the forearm. If the reaction was negative forty-eight hours later, a dose of 0.005 mg. PPD was injected into the skin of the opposite arm and a second reading was made at forty-eight hours thereafter.

The same preparation of PPD (trichloracetic acid preparation), kindly supplied by

[1] From The Henry Phipps Institute, University of Pennsylvania; and the Branch of Health, Bureau of Indian Affairs, Department of the Interior, Washington, D. C.

Dr. Florence Seibert, Henry Phipps Institute, was used for the first five years of the study, after which time another sample designated as PPD-S (ammonium sulfate preparation), also supplied by Dr. Seibert, was used.

The required dilutions were prepared daily from the concentrated PPD solution with sterile physiologic saline and were not used when more than twenty-four hours old. The injections of tuberculin and the interpretation of the reactions were made, with but few exceptions, by the same persons throughout the study.

Following the tuberculin testing in each geographic area, all persons less than twenty years of age who failed to react to both 0.00002 and 0.005 mg. of PPD were first graded by year of birth and sex and then divided by alternation into two approximately equal groups.

One group received an intracutaneous injection of either 0.1 or 0.15 mg., moist weight, of one of thirteen different lots of freshly prepared BCG vaccine into the skin over the region of the deltoid muscle. This vaccine was suspended in physiologic saline and was always used within seventy-two hours after preparation.

The second group received an intracutaneous injection of physiologic saline in the same location and served as controls.

The BCG-vaccinated group consisted of 737 males and 814 females, a total of 1,551 persons; while the control group consisted of 738 males and 719 females, a total of 1,457 persons. At the beginning of the program both groups ranged in age from less than one year to nineteen years, inclusive.

Of the 3,008 vaccinated persons and controls included in this study, approximately 85 per cent were examined roentgenographically at the time of, or soon after, the injection of the BCG vaccine or physiologic saline. Both groups were examined at approximately annual intervals by means of the tuberculin test and chest roentgenograms.

From 1936 to 1941, inclusive, annual roentgenographic examinations were performed on 91.2 to 97.4 per cent of the vaccinated group and 91.5 to 96.8 per cent of the controls. From 1942 to 1944, the number of persons examined roentgenographically decreased to a low of 69 per cent of those vaccinated and 72.1 per cent of the controls, as a result of conditions associated with World War II. In 1944 and 1945, the field examinations were discontinued but, during 1946 and 1947, tuberculin testing and roentgenographic examinations were conducted once more at all agencies, and a total of 80.2 per cent of those vaccinated and 78.2 per cent of the controls were examined roentgenographically. By 1946 to 1947, re-examinations had been made on Rosebud Agency, South Dakota, and in southeastern Alaska for the ninth year after the initiation of the study in those areas, and for the tenth and eleventh years in the remaining areas.

The roentgenograms were originally interpreted by an experienced radiologist soon after they were taken, and were identified solely by agency and number. The interpretation of the roentgenograms served as an index of the annual morbidity from tuberculosis in the BCG-vaccinated and control groups. An interim report of the roentgenographic findings has been presented previously (1, 2, 3).

With the completion of the roentgenographic examinations and tuberculin testing in 1946 to 1947 in all areas, it was decided to terminate the annual field examination phase of this study. All films were transferred to the Henry Phipps Institute and filed alphabetically by agency without regard to whether they represented a vaccinated person or a control case. Each individual envelope contained all films of that person taken during the course of the study.

OBSERVATIONS

Procedure

As the question of bias might be raised regarding the method of selecting and interpreting the films, a pilot study was carried out with the roentgenograms of the Shoshone and Arapaho Indians of the Wind River Agency, Wyoming. These roentgenograms were interpreted by two different procedures. The first procedure was to read all of the films of any one year in alphabetical order for the eleven years of the study. When this year-by-year review was completed, a second method was carried out in which all of the films for any one person were read serially in chronologic order and alphabetically for each agency. It was found that with the second procedure of serial examination a diagnosis of tuberculosis or suspected tuberculosis based on the first method of reading single annual films could not be substantiated in 18.8 per cent of cases so diagnosed. Because of this difference, the plan of interpreting the individual films serially in alphabetical order and by agency was adopted as a more accurate method.

The question might be raised concerning the quality of the roentgenograms, since they represent a single antero-posterior view taken in the vast majority of cases, under field conditions with a 30-milliampere portable X-ray unit powered by a portable 3-kilowatt electric generating unit. Surprisingly enough, the quality of the films compared favorably with those taken with a 300-milliampere fixed X-ray unit. In any event the quality of the roentgenograms was the same for both the vaccinated and control groups.

It is well recognized that subjective errors in the interpretation of the films will occur. These errors will, in large part, depend upon the training, clinical and roentgenographic experience, and visual acuity of the radiologist. In this study the subjective errors would be uniform for both groups, since one of the investigators (SCS), who had no previous association with the study, personally interpreted all of the films as objectively as possible and with no knowledge of the history of the case or of the tuberculin reaction.

The name and location of each agency or area studied, the tribes represented, the date when roentgenographic examinations were initiated, and the date when they were last obtained, as well as the number of persons and the total number of roentgenograms for the BCG-vaccinated and control groups, are all summarized in table 1.

During the course of the study an average of 8.86 and 8.9 roentgenograms were taken of each of the BCG-vaccinated persons and controls, respectively. This indicates that both groups were examined roentgenographically to the same degree. The discrepancy between the original numbers included in this study and the number subsequently followed by means of roentgenographic examination may be attributed to deaths occurring before a chest roentgenogram could be obtained, to the fact that a very few persons were not found after the initial examination, and to the loss of several files of films.

The present study is based on the interpretation of a total of 13,660 films of

1,541 BCG-vaccinated persons and 12,920 films of 1,451 unvaccinated controls collected during nine to eleven years of observation. Not every person in this study was examined roentgenographically every year, since some failed to appear for one reason or another, but subsequent roentgenographic examinations indicated what pathologic changes, if any, had occurred in the interim.

The interpretation of roentgenographically demonstrable pulmonary lesions on an etiologic basis is frequently difficult, and is increasingly so in the absence of clinical history and laboratory data. In view of this, and with a realization of the protean nature of the pulmonary lesions of tuberculosis, as well as the absence

TABLE 1

NUMBER OF BCG-VACCINATED AND CONTROL PERSONS EXAMINED ROENTGENOGRAPHICALLY BY AGENCY AND BY TRIBE FROM 1936 TO 1946, INCLUSIVE

NAME AND LOCATION OF AGENCY	NAME OF TRIBE	MONTH AND YEAR STUDY WAS INITIATED	MONTH AND YEAR LAST OBSERVED	BCG-VACCINATED			CONTROLS		
				Number Vaccinated	Number Examined Roentgenographically	Total Number of Roentgenograms	Number of Controls	Number Examined Roentgenographically	Total Number of Roentgenograms
Pima, Ariz.	Pima	February, 1936	May, 1947	258	256	2,482	263	253	2,615
Wind River, Wyo.	Shoshone	July, 1936	June, 1947	110	108	1,017	85	85	796
Wind River, Wyo.	Arapaho	July, 1936	June, 1947	118	118	1,177	106	103	1,020
Turtle Mt., N. D.	Chippewa	October, 1936	November, 1946	170	168	1,657	162	161	1,610
Pima, Ariz.	Pima	February, 1937	May, 1947	96	96	883	86	85	799
Rosebud, S. D.	Sioux	October, 1937	October, 1946	301	299	2,451	291	291	2,444
Alaska	Tlingit	January, 1938	January, 1947						
	Haida	January, 1938	January, 1947	498	496	3,993	464	463	3,636
	Tsimshian	January, 1938	January, 1947						
				1,551	1,541	13,660	1,457	1,451	12,920

of criteria specific for tuberculosis, one of the investigators (SCS) interpreted the films and classified them in accordance with the 1950 edition of *Diagnostic Standards and Classification of Tuberculosis* of the National Tuberculosis Association.

Diagnostic Criteria

A diagnosis of tuberculosis was made when the film showed soft or flocculent spots more or less localized with ill-defined hazy borders, or sharply defined, strandlike lesions, or both. The diagnosis of caseation was based on the appearance of areas of rarefaction usually located in the apical region. Calcification was diagnosed on the appearance of sharply defined areas of varying density which usually approximated the density of bone.

No absolute line of demarcation can be drawn between the primary and reinfection type of pulmonary tuberculosis, especially in adults. Nevertheless, an attempt was made to differentiate between primary and reinfection types of tuberculosis.

The lesion of primary tuberculosis may be so nearly insignificant that it cannot be demonstrated on either physical or roentgenographic examination. The lesion may be situated in any part of the lung parenchyma, but is usually located in the subpleural

region. Roentgenographically, the lesion can be identified as a small patch of coalescing light or flocculent spots. The extent of the lesion varies from several small light spots to a frank pneumonic process, at times involving a large part of the lobe. In the vast majority of cases a single focus of involvement occurs. In children, the primary lesion noted in the lung parenchyma is usually associated with enlargement of the ipsolateral tracheobronchial lymph nodes. In the present study the criterion for diagnosing primary tuberculosis was either the presence of an abnormal shadow in the lung parenchyma associated with enlargement of hilar nodes or the occurrence of either type of lesion independently with subsequent appearance of either fibrous strands or calcification of the original lesion. When the roentgenographic interpretation was doubtful concerning the chronicity of the lesion or in the absence of either fibrous strands or calcification, the case was classified as suspected primary tuberculosis. In adults, the lesion of primary infection differed from that noted in the younger age group in that enlargement of the tracheobronchial nodes was slight or not demonstrable roentgenographically, while the parenchymal lesions simulated the reinfection type of tuberculosis. The present writers are in accord with the observations of High and Zwerling (5) that the calcification following tuberculous infection is most frequent among the younger age group.

A diagnosis of reinfection tuberculosis was made when two or more successive annual films showed shadows compatible with such a diagnosis. These lesions were further classified as *minimal*, *moderately advanced*, or *far advanced*.

A diagnosis of miliary tuberculosis was based on finding more or less uniformly distributed, fine, more or less rounded shadows throughout the lungs.

Lesions were classified as pleural effusions when the roentgenogram showed obliteration of the phrenicocostal angle with extensive diffuse cloudiness of the corresponding lung field.

Sharply defined, single or multiple, uniform or mottled areas having the density of the rib were classified as calcifications.

In some instances the observed shadows were not sufficiently characteristic to permit a definite diagnosis of tuberculosis. Such lesions were at first interpreted as nontuberculous abnormalities. When two or more successive films showed such shadows, which, however, disappeared on subsequent roentgenographic examination, the lesions were classified as either suspected primary or suspected reinfection tuberculosis.

A diagnosis of nontuberculous pulmonary lesion was made when the shadows conformed with the generally accepted roentgenographic characteristics of lobar, broncho- or atypical pneumonia. These lesions invariably presented roentgenographic evidence of rapid clearing. A diagnosis of "negative" was made when the roentgenograms showed no abnormal shadows. The final definite classification of the pulmonary lesions was based on the roentgenogram which showed the most advanced stage of the disease.

RESULTS

Prevalence of Pulmonary Lesions

The distribution of both tuberculous and nontuberculous pulmonary lesions in the BCG-vaccinated and control groups by type of lesion, agency, and tribe is summarized in table 2.

It is evident from table 2 that primary tuberculosis was the most frequent manifestation of the disease both among the vaccinated persons and among the control group. This form of tuberculosis was conspicuously frequent among the control group of Arapaho Indians of the Wind River Agency, Wyoming; among

the vaccinated persons and control group of the Sioux Indians of Rosebud Agency, South Dakota; and among the control group living in southeastern Alaska.

The high incidence of primary tuberculosis among the vaccinated group of the Rosebud Sioux Indians can be attributed to the low antigenic value of the BCG vaccine used at this agency. Previous studies (6) have shown that, of the 13 lots of BCG vaccine used in this investigation, vaccine lots 8 and 9, prepared from slowly growing, rough dry colonies, were the least antigenic. Of those vaccinated with BCG vaccine lots 8 and 9, only 13.4 and 15.6 per cent, respectively, reacted to 0.00002 mg. of the original trichloracetic acid PPD one year after vaccination, while of those vaccinated with the 11 other lots of vaccine, 33.3 to 61.4 per cent reacted to 0.00002 mg. of the same preparation of PPD after the same interval.

The marked differences in the incidence of primary tuberculosis among the 85 Shoshone Indians and the 106 Arapaho Indians who served as controls suggests that there exists a difference in the resistance to tuberculosis among these two Indian tribes. This may be a racial factor or it may be due to differences in the degree of exposure. The Shoshone Indians and the Arapaho Indians both live on the Wind River Agency. The former occupy the west side of the agency; the latter, the east side. The Shoshones have inhabited this part of the United States from time immemorial, while the Arapahoes were transferred to this agency in 1887. Because of past traditions there have been but few intermarriages between the members of the two tribes. The Shoshones are of the Shoshonean stock and linguistically belong to the Uto-Aztecan group. Physically, they tend to be short and stocky and overweight. The incidence of bacterial infections, expecially those due to *Streptococci*, is low. Extrapulmonary tuberculosis was not observed among these Indians. The Arapaho Indians are of Algonquian stock. Physically, they tend to be tall and slim and underweight. The incidence of bacterial infections, especially streptococcal infections, is relatively high, as is the incidence of extrapulmonary forms of tuberculosis. Both tribes farm and raise livestock as a means of livelihood. Their socio-economic conditions and housing are approximately the same.

In table 2 are presented, not only the difference in the incidence of primary tuberculosis among all groups studied, but the data on other forms of tuberculosis. The incidence of minimal and moderately advanced tuberculosis and of pleural effusions is significantly higher among the controls than among the vaccinated of the different agencies. The number of cases of far advanced tuberculosis is too small to be statistically significant.

The cases of miliary tuberculosis reported in table 2 include only those persons who showed roentgenographically demonstrable pulmonary lesions, and do not represent all deaths from miliary tuberculosis which occurred during the course of this study. Excluded from the study are those cases of miliary tuberculosis in which the last roentgenogram failed to show any demonstrable pulmonary lesion of tuberculosis. No instances of miliary tuberculosis were observed among those who had received BCG vaccine.

Pleural effusions were noted more frequently among the control group than among the vaccinated group. In the absence of clinical and laboratory data such

TABLE 2

INCIDENCE OF ROENTGENOGRAPHICALLY DEMONSTRABLE PULMONARY LESIONS IN BCG-VACCINATED AND UNVACCINATED PERSONS BY AGENCY AND TYPE OF LESION

TYPE OF PULMONARY LESION		AGENCY AND TRIBE															
		Pima A		Shoshone		Arapaho		Turtle Mt.		Pima B		Rosebud		Alaska		Total	
		Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Primary	V	3	1.9	1	0.9	2	1.7	2	1.2	1	1.0	15	5.1	14	2.8	40	2.60
	C	6	3.2	2	2.3	23	22.4	6	4.9	1	1.2	30	10.3	69	14.9	141	9.72
Minimal	V	3	1.2	1	0.9	0	—	0	—	0	—	0	—	7	1.4	11	0.71
	C	4	1.5	2	2.3	0	—	3	1.9	1	1.2	6	2.1	15	3.2	31	2.14
Moderate	V	0	—	0	—	0	—	0	—	0	—	1	0.3	1	0.2	2	0.13
	C	2	0.7	4	4.8	2	1.9	3	1.9	1	1.2	2	0.7	6	1.3	20	1.37
Far advanced	V	0	—	0	—	0	—	0	—	0	—	1	0.3	0	—	1	0.06
	C	1	0.3	1	1.2	1	0.9	0	—	0	—	0	—	0	—	3	0.20
Miliary	V	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—
	C	1	0.3	0	—	3	2.9	0	—	1	1.2	0	—	5	1.1	10	0.68
Pleural effusion	V	2	0.8	0	—	1	0.8	0	—	0	—	2	0.6	5	1.0	10	0.65
	C	8	3.2	1	1.2	2	1.9	0	—	1	1.2	8	2.7	13	2.8	33	2.28
Calcification	V	46	17.8	0	—	2	1.7	4	2.4	24	25.0	6	2.0	2	0.4	84	5.45
	C	34	12.9	2	2.3	10	9.7	6	3.8	12	14.0	8	2.7	10	2.1	82	5.65
Suspected primary	V	2	0.8	3	2.8	3	2.5	0	—	1	1.0	4	1.3	3	0.6	16	1.04
	C	0	—	2	2.3	6	5.8	1	0.6	1	1.2	6	2.1	11	2.3	27	1.86
Suspected reinfection	V	3	1.2	0	—	8	6.8	4	2.4	0	—	1	0.3	0	—	16	1.04
	C	3	1.1	4	4.8	1	0.9	1	0.6	1	1.2	5	1.7	10	2.1	25	1.72
Nontuberculous	V	6	2.3	14	13.0	13	11.0	10	5.9	4	4.1	12	4.0	18	3.6	77	5.00
	C	15	5.7	5	7.0	6	5.8	12	7.4	3	3.5	16	5.5	23	4.9	81	5.59
Negative	V	189	74.0	89	82.4	89	75.5	148	88.1	66	68.9	257	86.1	446	90.0	1,294	83.32
	C	187	71.1	61	71.8	49	47.8	127	78.9	63	74.1	210	72.2	301	65.3	998	68.80

V = Vaccinated.
C = Controls.

effusions have been arbitrarily classified as being of tuberculous etiology. The possibility that pleural effusions among those living on the Pima Agency, Arizona, may be due to coccidioidomycosis cannot be excluded.

Except in the Pima Agency, Arizona, pulmonary calcifications occurred more frequently among the control group than among the vaccinated group. The incidence of such lesions was relatively low and the lesions were uniformly distributed among the different agencies except at the Pima Agency. Among the Pima Indians, as seen in table 2, pulmonary calcification was significantly more frequent in both groups than among those living on the other agencies and is somewhat higher among the vaccinated. The investigations of Aronson, Saylor, and Parr (7), in which pulmonary calcification was found in a significant number of tuberculin-negative coccidioidin reactors on the Pima Agency, are pertinent to this problem. Their observations indicate that the high incidence of pulmonary calcifications on the Pima Agency may be due to coccidioidomycosis rather than to tuberculosis. Since the present study is based solely on the interpretation of the roentgenogram, all calcifications have been grouped together and have been arbitrarily excluded from the category of tuberculous lesions for the purpose of this study.

Pulmonary lesions in the categories of suspected primary, suspected reinfection tuberculous, and nontuberculous lesions were somewhat more frequent among the control group than among the vaccinated group.

Abnormal roentgenographically demonstrable pulmonary shadows from all causes were noted in 16.7 per cent of the BCG-vaccinated group and in 31.2 per cent of the control group. Definite pulmonary lesions of tuberculosis, classified as primary, minimal, moderately advanced, far advanced, miliary tuberculosis, and pleural effusions, were observed in 4.1 per cent of the vaccinated persons and in 16.4 per cent of the control group.

Annual Attack Rate

A more accurate analysis of the morbidity from tuberculosis can be made by determining the annual attack rate. This rate was determined by first excluding from the calculations the 14 BCG-vaccinated persons and 23 control persons whose initial films, obtained either at the start of the study or within the first year, presented roentgenographic evidence of pulmonary tuberculosis. For each of the subsequent years, the number of persons exposed to risk was obtained by subtracting from the previous year the number of persons who had developed tuberculosis plus those persons who were lost to the study because of death or who were not available for subsequent roentgenographic examinations. The attack rate was then calculated on the basis of the number of new cases of tuberculosis which developed within a given year in the population at risk. The decrease in the number at risk is cumulative with increasing years of observation. The cumulative attack rate per year from pulmonary tuberculosis for both the BCG-vaccinated and the control groups is presented in table 3.

In table 3 may also be seen the probability of the initial population remaining free from tuberculous pulmonary lesions and its complementary probability,

that of developing such lesions. These probabilities were derived by multiplying the per cent of persons who remained roentgenographically "negative" at the end of a given year by the per cent of persons who remained "negative" the succeeding year. For example, among the BCG-vaccinated group, 99.275 per cent were roentgenographically "negative" at the end of the first year and 99.132 per cent of these "negatives" were "negative" at the end of the second year of observation. The per cent of the initial population who therefore remained roentgenographically "negative" through the two years was 0.99132 of 99.275 or 98.41. The probability of developing pulmonary tuberculosis at the end of the second year was the difference between the per cent of persons who remained "negative" and 100 per cent or 1.59.

TABLE 3

INCIDENCE OF ROENTGENOGRAPHICALLY DEMONSTRABLE TUBERCULOUS PULMONARY LESIONS IN BCG-VACCINATED AND CONTROL PERSONS BY YEAR OF OBSERVATION

	BCG-VACCINATED							CONTROLS						
Years Observed	Total Number	Number Missing	Roentgenographically Positive		Per Cent Roentgenographically Negative	Probability of Becoming		Total Number	Number Missing	Positive		Per Cent Roentgenographically Negative	Probability of Becoming	
			Number	Per Cent		Roentgenographically Negative	Roentgenographically Positive			Number	Per Cent		Roentgenographically Negative	Roentgenographically Positive
1	1,517	8	11	0.725	99.275	99.28	0.72	1,421	13	22	1.55	98.45	98.45	1.55
2	1,498	10	13	0.868	99.132	98.41	1.59	1,386	13	30	2.20	97.80	96.28	3.72
3	1,475	14	4	0.271	99.729	98.15	1.85	1,343	14	31	2.31	97.69	94.06	5.94
4	1,457	33	5	0.343	99.657	97.81	2.19	1,298	27	29	2.24	97.76	91.95	8.05
5	1,419	66	3	0.211	99.789	97.60	2.40	1,242	71	31	2.50	97.50	89.65	10.35
6	1,350	114	4	0.315	99.685	97.30	2.70	1,140	117	31	2.76	97.24	87.18	12.82
7	1,232	61	3	0.264	99.736	97.04	2.96	991	53	17	1.72	98.28	85.68	14.32
8	1,168	72	3	0.321	99.679	96.73	3.27	921	69	10	1.09	98.91	84.78	15.22
9	1,093	489	2	0.252	99.748	96.48	3.52	841	0	9	1.14	98.86	83.78	16.22
10	602	234	0	—	—	—	—	432	1	3	0.71	99.29	83.19	16.81
11	368	0	0	—	—	—	—	270	0	1	0.46	99.54	82.81	17.19

It will be noted from table 3 that, among the BCG-vaccinated persons, the highest attack rate occurred during the first two years after vaccination, after which time it declined rapidly and maintained a relatively constant rate throughout the period of observation. Even during the first two years after vaccination the attack rate among the BCG-vaccinated group was less than half that of the control group.

During the period covered by the present study, the attack rate from pulmonary tuberculosis was significantly higher among the control group than among the BCG-vaccinated group. This was especially so during the first six years of observation. The probability of developing pulmonary tuberculosis, which is cumulative with increasing periods of observation, was 3.52 for the vaccinated persons and 17.19 for the control group at the end of eleven years of observation. The homogeneity of the population at risk of both the BCG-vac-

cinated group and the control group is indicated by the fact that 378 from each group were lost because of death or for other reasons.

The attack rate of nontuberculous pulmonary lesions in both groups was determined in a similar manner. Excluded from the calculations were the 58 (3.7 per cent) nontuberculous lesions observed on the initial films of the BCG-vaccinated group and the 37 (2.5 per cent) nontuberculous lesions noted on the initial films of the controls. The attack rate per year and the probability of developing nontuberculous pulmonary lesions per year are presented in table 4.

TABLE 4

INCIDENCE OF ROENTGENOGRAPHICALLY DEMONSTRABLE NONTUBERCULOUS PULMONARY LESIONS IN BCG-VACCINATED AND CONTROL PERSONS BY YEAR OF OBSERVATION

	BCG-VACCINATED							CONTROL						
Years Observed	Total Number	Number Missing	Roentgenographically Positive		Per Cent Roentgenographically Negative	Probability of Becoming		Total Number	Number Missing	Roentgenographically Positive		Per Cent Roentgenographically Negative	Probability of Becoming	
			Number	Per Cent		Roentgenographically Negative	Roentgenographically Positive			Number	Per Cent		Roentgenographically Negative	Roentgenographically Positive
1	1,475	8	28	1.898	98.102	98.102	1.90	1,406	13	29	2.062	97.938	97.938	2.06
2	1,439	12	31	2.154	97.846	95.988	4.01	1,364	17	18	1.319	98.681	96.646	3.36
3	1,396	13	16	1.146	98.854	94.887	5.11	1,329	18	23	1.730	98.270	94.974	5.03
4	1,367	32	17	1.243	98.757	93.707	6.30	1,288	36	25	1.940	98.060	93.131	6.87
5	1,318	65	8	0.606	99.394	93.139	6.86	1,237	70	25	2.021	97.979	91.248	8.75
6	1,245	107	14	1.124	98.876	92.092	7.91	1,142	118	18	1.576	98.424	89.809	10.19
7	1,124	84	11	0.978	99.022	91.191	8.81	1,006	45	10	0.994	99.006	88.916	11.08
8	1,050	57	5	0.472	99.528	90.760	9.24	951	67	9	0.946	99.054	88.074	11.92
9	997	554	3	0.300	99.700	90.487	9.51	875	465	8	0.914	99.086	87.269	12.73
10	440	142	1	0.227	99.773	90.281	9.72	402	145	4	0.995	99.005	86.400	13.60
11	297	0	1	0.336	99.664	89.977	10.02	253	0	3	1.185	98.815	85.376	14.62

The attack rate of nontuberculous pulmonary lesions fluctuated from year to year and was higher among the control group than among the BCG-vaccinated group, especially during the last four years of the study. The probability of developing nontuberculous pulmonary lesions at the end of the eleven years of observation was 10.02 for the vaccinated group and 14.62 for the control group. Figure 1 presents graphically the probability on an annual basis of developing roentgenographically demonstrable tuberculous as well as nontuberculous pulmonary lesions for both the vaccinated group and the control group.

Evolution, Course, and Duration of Pulmonary Lesions

Pulmonary lesions, both tuberculous and nontuberculous, developed in approximately the same manner in both the vaccinated group and control group. The course of the pathologic processes as determined roentgenographically showed no conspicuous differences. The duration of the lesion was determined from the time the lesion was first diagnosed until it had healed, as measured by calcification, fibrosis, stabilization of the lesion, or complete clearing of the pathologic process. In some instances the pulmonary lesion was first observed late in the course of the study and was not observed for a long enough period to permit

a definite diagnosis. Pulmonary lesions diagnosed as primary persisted in 70 per cent of the cases for one to three years in both the vaccinated group and the control group. Among the BCG-vaccinated persons, lesions of minimal tuberculosis persisted for one to three years in 63 per cent of the cases, while among the control group such lesions persisted for the same period in 57 per cent of the cases.

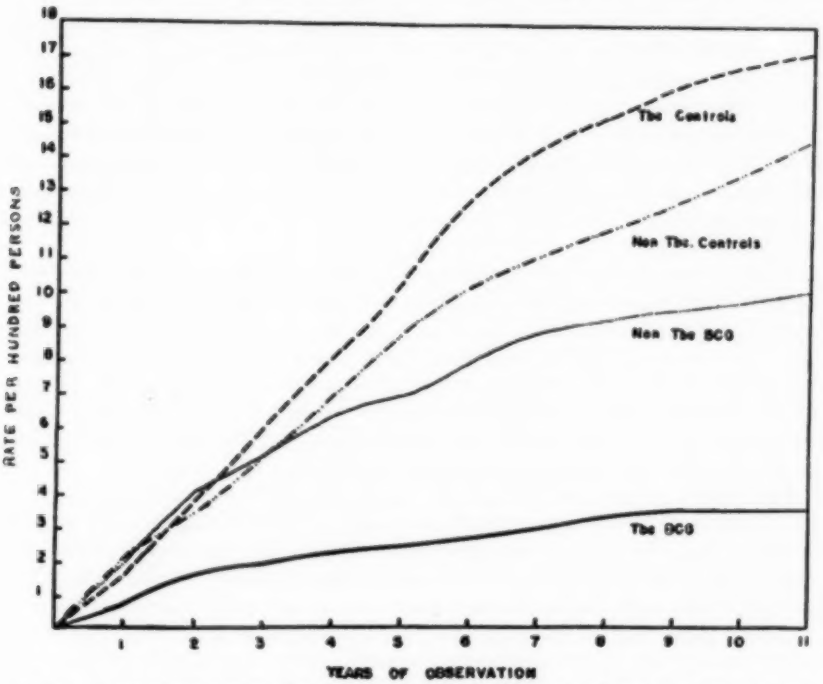


FIG. 1. Rate of occurrence of roentgenographically demonstrable tuberculous and nontuberculous pulmonary lesions in BCG-vaccinated and control persons.

The number of cases of moderately advanced and far advanced tuberculosis among the vaccinated persons is too small to permit drawing any comparison. Miliary tuberculosis was not observed among the vaccinated group. Among the control group, the 10 persons with miliary tuberculosis died within two years after the diagnosis was established. Pleural effusions persisted for one to two years in 90 per cent of those vaccinated and the control persons so diagnosed. Calcifications once observed persisted throughout the course of the study. In general, nontuberculous lesions usually did not persist as long as tuberculous lesions, except in the rare instances of bronchiectasis.

Relation of Age and Sex to Occurrence of Pulmonary Lesions

It is generally recognized that the pathologic character, distribution, clinical course, prognosis, and epidemiology of tuberculosis may vary at different ages.

Because of these variations, the lesions of pulmonary tuberculosis have been classified as primary or childhood type and reinfection or adult type. With the decrease in tuberculous infection in recent years, especially in the younger age groups, primary tuberculosis is occurring more frequently in adult life. A unique opportunity of studying the type of pulmonary tuberculosis in relation to age was made possible in this study, since roentgenograms were made annually for a period of nine to eleven years in a population ranging in age at the beginning of the study from less than one year to nineteen years. A correlation has been made of the type of pulmonary lesion, both tuberculous and nontuberculous, at the time of its first roentgenographic appearance with the attained age of the persons. For this purpose the attack rate for each type of pulmonary lesion has been calculated on the basis of 1,000 person-years of observation for each quinquennium of attained age. The attack rate of both tuberculous and nontuberculous pulmonary lesions for the vaccinated and control groups is presented in five-year age periods in table 5.

It will be noted from table 5 that certain types of tuberculosis occurred most frequently at certain age periods. These findings conform to the generally accepted views on this subject. Thus, the attack rate for primary tuberculosis for both the vaccinated persons and the control group was highest in the younger age groups and the incidence decreased rapidly with increasing age. In all age groups the attack rate of primary tuberculosis was significantly lower among the vaccinated persons than among the control group, and the decrease in the rate of attack with increasing age was greater among those vaccinated.

Reinfection type of pulmonary tuberculosis classified as minimal, moderately advanced, and far advanced manifested itself with increasing frequency with increasing age. As with primary tuberculosis, the rate of attack was significantly higher among the control group than among the vaccinated group. Miliary tuberculosis occurred in all age groups after five years, but the number of cases is too small to be statistically significant. Pleural effusions occurred most frequently in the ten- to fourteen- and fifteen- to nineteen-year age groups. The rate of attack was significantly higher among the control group than among the vaccinated persons. Calcified pulmonary nodules occurred with equal frequency in the two groups and were most common in the first decennium. Pulmonary lesions diagnosed as suspected primary tuberculosis were found more frequently among the control persons of the younger age groups. Suspected reinfection type tuberculosis was highest among the vaccinated persons less than five years of age. Thereafter, it was noted more frequently among the control groups.

Studies of the mortality rate from tuberculosis indicate definite differences in the two sexes. This is especially marked at the age of puberty. Putnam (8) has analyzed the mortality from tuberculosis in the United States according to sex for the period from 1870 to 1920. She found that the death rate from this disease was higher among females during the age period five to twenty-four and that this difference was most marked during the age period of ten to fourteen. Aronson and Aronson (4) found that 3.2 per cent of 738 unvaccinated males who ranged in age from less than one year to nineteen years at the beginning of the

TABLE 5

OCCURRENCE OF TUBERCULOUS AND NONTUBERCULOUS PULMONARY LESIONS, IN FIVE-YEAR AGE PERIODS, PER 1,000 PERSON YEARS

AGE IN FIVE-YEAR PERIODS	GROUP	PERSON-YEARS OBSERVED	PRIMARY TUBERCULOSIS		MINIMAL TUBERCULOSIS		MODERATELY ADVANCED TUBERCULOSIS		FAR ADVANCED TUBERCULOSIS		MILIARY TUBERCULOSIS		PLEURAL EFFUSION		CALCIFICATION		SUSPECTED PRIMARY		SUSPECTED REINFECTION		NON-TUBERCULOUS	
			Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Under 5	V	1,327	9	6.77	0	—	0	—	0	—	0	—	0	—	1	0.75	3	2.26	8	6.03	15	11.30
	C	1,292	20	15.48	0	—	0	—	0	—	0	—	0	—	0	—	4	3.09	0	—	10	7.74
5 to 9	V	4,063	15	3.69	0	—	0	—	0	—	0	—	1	0.24	31	7.63	6	1.47	1	0.24	27	6.64
	C	3,766	53	14.07	2	0.53	0	—	0	—	2	0.53	5	1.32	26	6.90	4	1.06	7	1.86	12	3.19
10 to 14	V	5,552	12	2.16	4	0.72	0	—	0	—	0	—	7	1.26	38	6.88	5	0.90	2	0.36	18	3.24
	C	5,084	48	9.44	9	1.77	8	1.57	0	—	4	0.78	14	2.77	35	6.88	9	1.77	8	1.57	32	6.29
15 to 19	V	3,996	4	1.00	4	1.00	0	—	1	0.25	0	—	2	0.50	12	3.00	1	0.25	4	1.00	15	3.78
	C	3,669	19	5.12	20	5.45	9	2.45	1	0.27	2	0.54	11	2.99	18	4.91	8	2.18	9	2.45	24	6.66
20 to 24	V	1,301	0	—	2	1.53	2	1.53	0	—	0	—	0	—	2	1.53	1	0.77	1	0.77	3	1.53
	C	1,185	1	0.84	0	—	3	2.61	2	1.69	1	0.84	3	2.61	3	2.61	2	1.69	1	0.84	3	2.61
25 to 29	V	130	0	—	1	0.71	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—
	C	132	0	—	0	—	0	—	0	—	1	7.57	0	—	0	—	0	—	0	—	0	—

V = Vaccinated.
C = Control.

TABLE 6

OCCURRENCE OF PULMONARY LESIONS IN BCG-VACCINATED AND CONTROL PERSONS ACCORDING TO SEX

TYPE OF PULMONARY LESION	GROUP	SEX				TOTAL	
		Males		Females			
		Number	Per Cent	Number	Per Cent	Number	Per Cent
Primary	V	19	2.6	21	2.6	40	2.6
	C	63	8.9	78	10.8	141	9.7
Minimal	V	5	0.7	6	0.6	11	0.7
	C	10	1.4	21	2.9	31	2.1
Moderate	V	0	—	2	0.2	2	0.13
	C	7	1.0	13	1.8	20	1.3
Far advanced	V	1	0.1	0	—	1	0.06
	C	2	0.2	1	0.1	3	0.21
Miliary	V	0	—	0	—	0	—
	C	3	0.4	7	0.9	10	0.7
Pleural effusion	V	7	0.9	3	0.4	10	0.6
	C	16	2.2	17	2.4	33	2.3
Calcification	V	35	4.9	49	6.0	84	5.4
	C	43	5.9	39	5.4	82	5.6
Suspected primary	V	4	0.5	12	1.5	16	1.0
	C	13	1.8	14	1.9	27	1.8
Suspected reinfection	V	9	1.3	7	0.8	16	1.0
	C	11	1.5	14	1.9	25	1.7
Nontuberculous	V	33	4.6	44	5.4	77	4.9
	C	33	4.5	48	6.7	81	5.6
Summary							
Tuberculous lesions	V	32	4.4	32	3.9	64	4.1
	C	101	13.8	137	18.9	238	16.4
Nontuberculous lesions	V	81	11.2	112	13.7	193	12.5
	C	100	13.8	115	15.9	215	14.8

study died from tuberculosis during the course of their nine to eleven years of observation. Among 719 unvaccinated females of comparable age observed during the same period of time and living under comparable conditions, 5.7 per cent died from the disease.

In table 6 is presented the distribution by sex of the different types of pulmo-

nary lesions, both tuberculous and nontuberculous, in the BCG-vaccinated and control groups. In the control group the incidence of primary, minimal, moderately advanced, and miliary tuberculosis was higher among the females than the males; while pleural effusions, suspected tuberculosis, and nontuberculous pulmonary lesions occurred with the same frequency in both sexes. On the other hand, among the BCG-vaccinated persons, the incidence of primary and minimal tuberculosis was the same among males and females, while pleural effusions were significantly lower among the BCG-vaccinated females. Pulmonary lesions diagnosed as suspected primary were observed more frequently among the females and suspected reinfection tuberculosis more often among the males. Nontuberculous pulmonary lesions among the BCG-vaccinated persons occurred with the same degree of frequency in both males and females.

DISCUSSION

It is difficult to evaluate the protective role of any immunizing agent in the control of tuberculosis in man, in view of the rapidly falling mortality from this disease. The observations made in the course of the present study indicate that BCG vaccination does induce increased resistance against infection with virulent tubercle bacilli. It was found that the morbidity from pulmonary tuberculosis, as determined from serial roentgenograms made at approximately annual intervals, was significantly lower among those who had received BCG vaccine than among the untreated controls.

As tuberculous pulmonary lesions cannot be differentiated roentgenographically in every instance from nontuberculous pulmonary lesions, the incidence of nontuberculous pulmonary lesions in both the BCG-vaccinated and control groups have been compared. It was found during the period of observation that nontuberculous pulmonary lesions occurred somewhat more frequently among the control group than among the vaccinated persons. This difference in the incidence of nontuberculous lesions in the two groups was not as significant as was the difference in the occurrence of tuberculous lesions.

Further proof of the specific protective value of BCG vaccine is indicated by the observations that, among the BCG-vaccinated persons, the highest incidence of tuberculous pulmonary lesions was noted among those who had been injected with two lots of BCG vaccine of low antigenicity, prepared from slowly growing cultures on veal potato medium instead of on Sauton medium. The poor antigenic value of these preparations of vaccine was evidenced by the low incidence, 13.8 and 15.6 per cent, of persons who reacted to 0.00002 mg. of PPD tuberculin one year after vaccination.

Another point which lends support to the specific protective value of BCG vaccine is the fact that the morbidity from pulmonary tuberculosis among the BCG-vaccinated females was as low as or lower than that observed among the vaccinated males. On the other hand, among the unvaccinated females, the incidence of definite tuberculous pulmonary lesions was higher in the females than among the unvaccinated males. Other investigators have noted the higher mortality among young females in the general population.

SUMMARY

The incidence of tuberculous and nontuberculous pulmonary lesions was determined in 1,540 BCG-vaccinated and 1,450 unvaccinated persons. These two groups, negative to tuberculin at the beginning of the study, were comparable in age, sex, economic condition, and in the number of follow-up examinations.

The morbidity from tuberculosis was based on serial roentgenograms of the chest taken at approximately annual intervals for a period of nine to eleven years.

Pulmonary lesions presenting the roentgenographic characteristics of primary tuberculosis, minimal, moderately advanced, and far advanced tuberculosis, miliary tuberculosis, and pleural effusion were found in 64 (4.1 per cent) of the BCG-vaccinated persons and in 238 (16.4 per cent) of the control group.

Pulmonary lesions presenting the roentgenographic characteristics of suspected primary, suspected reinfection tuberculosis, nontuberculous lesions, and calcified nodules were found in 193 (12.5 per cent) of those vaccinated and in 215 (14.8 per cent) of the control group.

Primary lesions of tuberculosis were observed most frequently in the first decennium of life, while definite reinfection type tuberculosis and pleural effusions occurred most frequently in the second decennium.

Among the control group, the incidence of tuberculous pulmonary lesions was higher in the females than in the males; while, among the vaccinated persons, the incidence of such lesions was the same as or slightly lower among the females than among the males.

The highest incidence of pulmonary lesions among the BCG-vaccinated persons occurred among those who had received BCG vaccine of low antigenic value.

A comparison of the morbidity from pulmonary tuberculosis, as determined roentgenographically in BCG-vaccinated and control persons, gives added evidence of the protective value of BCG vaccine previously indicated by studies of the rate of mortality from tuberculosis in the same groups.

SUMARIO

La Ocurrencia de Lesiones Pulmonares en Personas Vacunadas y No Vacunadas con BCG

La incidencia de lesiones pulmonares tuberculosas y no tuberculosas fué determinada en 1,540 sujetos vacunados con BCG y 1,450 no vacunados. Esos dos grupos, ambos negativos a la tuberculina al iniciarse el estudio, eran comparables con respecto a edad, sexo, situación económica y número de exámenes subsiguientes.

La morbidad tuberculosa se basó en radiografías seriadas del pulmón, tomadas a plazos aproximados de un año durante un período de nueve a once años.

En 64 (4.1 por ciento) de los vacunados con BCG y en 238 (16.4 por ciento) de los testigos descubriéronse lesiones pulmonares que presentaban las características radiográficas de la tuberculosis primaria; tuberculosis mínima, moderadamente avanzada y muy avanzada; granulia; y derrame pleural.

En 193 (12.5 por ciento) de los vacunados y en 215 (14.8 por ciento) de los testigos, descubriéronse lesiones pulmonares que acusaban las características radiográficas de tuberculosis primaria sospechada, tuberculosis de reinfección sospechada, lesiones no tuberculosas y nódulos calcificados.

Las lesiones primarias de tuberculosis fueron observadas con la mayor frecuencia en el primer decenio de la vida, mientras que la tuberculosis de forma de reinfección bien definida y los derrames pleurales existían más frecuentemente en el segundo decenio.

Entre los testigos, la incidencia de lesiones tuberculosas del pulmón fué más alta en las mujeres que en los varones, en tanto que, entre los vacunados, la incidencia de dichas lesiones fué igual, o algo más baja, entre las mujeres que entre los varones.

La incidencia máxima de lesiones pulmonares entre los vacunados con BCG fué entre los que habían recibido vacuna BCG de bajo valor antigénico.

Una comparación de la morbidad debida a tuberculosis pulmonar, determinada radiográficamente en los becegetizados y los testigos, aporta nueva prueba del valor protector de la vacuna BCG, ya indicada antes por estudios de la tasa de mortalidad tuberculosa en los mismos grupos.

RESUME

Apparition de lésions pulmonaires chez des sujets vaccinés par le BCG et les non vaccinés

L'incidence de lésions pulmonaires tuberculeuses et non tuberculeuses fut déterminée 1.540 sujets vaccinés par le BCG et chez 1.450 sujets non vaccinés. Ces deux groupes anergiques à la tuberculine au début de l'étude, étaient comparables à l'égard de l'âge, du sexe, des conditions économiques et du nombre des examens périodiques ultérieurs.

La morbidité par tuberculose était basée sur des radiogrammes du poumon en série, répétés à intervalles d'un an pendant une période de neuf à onze ans.

Des lésions pulmonaires présentant les aspects radiologiques de la tuberculose primaire; de la tuberculose *a minima*, de formes dont l'évolution était modérément avancées ou très avancées; de la miliaire et de l'épanchement pleural ont été observées chez 64 (4,1%) des sujets vaccinés par le BCG et chez 238 (16,4%) des sujets témoins.

Des lésions pulmonaires présentant les images radiologiques d'une tuberculose primaire occulte, d'une réinfection probable, de lésions non tuberculeuses et de nodules calcifiés ont été observées chez 193 (12,5%) des sujets vaccinés et chez 215 (14,8%) des sujets témoins.

Les lésions primaires de la tuberculose ont été le plus fréquemment observées dans la première décade de la vie, alors que la fréquence des types de lésions de réinfection et les épanchements pleuraux a été plus grande dans la seconde décade.

Parmi les sujets témoins, l'incidence des lésions pulmonaires tuberculeuses était plus élevée chez les femmes que chez les hommes tandis que, chez les sujets vaccinés, l'incidence de ces lésions était la même ou légèrement plus faible chez les femmes que chez les hommes.

L'incidence la plus élevée des lésions pulmonaires parmi les sujets vaccinés par le BCG s'est manifestée chez ceux qui avaient reçu un vaccin BCG d'activité antigène faible.

Selon les déterminations radiologiques, l'étude comparative de la morbidité par tuberculose pulmonaire pratiquée chez des sujets vaccinés par le BCG et chez des sujets témoins a fourni une nouvelle preuve de la valeur protectrice du BCG, antérieurement indiquée par les études du taux de mortalité par tuberculose parmi des groupes semblables.

Acknowledgments

The advice and assistance of Mr. W. J. Carnahan, Research Secretary of the Philadelphia Tuberculosis and Health Association, and of Miss Mary H. Burke, Public Health Service, in the statistical analysis of this study are gratefully acknowledged.

REFERENCES

(1) Townsend, J. G., Aronson, J. D., Saylor, R., and Parr, I.: Tuberculosis control among the North American Indians, Am. Rev. Tuberc., 1942, *45*, 41.

(2) Aronson, J. D., and Palmer, C. E.: Experience with BCG vaccine in the control of tuberculosis among North American Indians, Pub. Health Rep., 1946, *61*, 802.

(3) Aronson, J. D.: Protective vaccination against tuberculosis, with special reference to BCG vaccination, Am. Rev. Tubere., 1948, *58*, 255.
(4) Aronson, J. D., and Aronson, C. F.: Appraisal of protective value of BCG vaccine, J.A.M.A. 1952, *149*, 334.
(5) High, R. H., and Zwerling, H. B.: Variation with age in the frequency of tuberculous pulmonary calcification, Pub. Health Rep., 1946, *61*, 1769.
(6) Aronson, J. D., Parr, I., and Saylor, R. M.: BCG vaccine: Its preparation and the local reaction to its injection, Am. Rev. Tubere., 1940, *42*, 651.
(7) Aronson, J. D., Saylor, R. M., and Parr, I.: Relationship of coccidioidomycosis to calcified pulmonary nodules, Arch Path., 1942, *34*, 31.
(8) Putnam, P.: Sex differences in pulmonary tuberculosis deaths, Am. J. Hyg., 1927, *7*, 663.

THE CORRELATION OF THE TUBERCULIN REACTION WITH ROENTGENOGRAPHICALLY DEMONSTRABLE PULMONARY LESIONS IN BCG-VACCINATED AND CONTROL PERSONS[1]

JOSEPH D. ARONSON AND CHARLOTTE FERGUSON ARONSON

(Received for publication June 15, 1953)

INTRODUCTION

In the previous paper Stein and Aronson (1) have presented data dealing with the incidence of roentgenographically demonstrable pulmonary lesions among 1,540 BCG-vaccinated persons and 1,450 unvaccinated controls who had been followed for a period of nine to eleven years.

The observed pulmonary lesions were classified as definitely tuberculous, suspect tuberculous, or nontuberculous, solely on the basis of an objective interpretation of serial roentgenograms obtained at approximately annual intervals. It has been found (2, 3, 4) that the diagnosis of pulmonary tuberculosis based solely on the interpretation of roentgenograms of the chest is subject to significant error even in the hands of well-qualified radiologists. In view of these findings and with an increasing appreciation of the nontuberculous nature of some pulmonary lesions which roentgenographically simulate tuberculosis, additional means must be considered for differentiating such pulmonary lesions. For this purpose the intracutaneous test with certain specific antigens can play an important part in establishing the specific nature of the lesion.

PLAN OF INVESTIGATION

An opportunity of evaluating the role of both tuberculin and coccidioidin in relation to roentgenographic findings offered itself in the course of a study initiated in 1936 to determine the specific protective value of BCG vaccine among some Indians of the United States and southeastern Alaska. During this study a group of 1,540 individuals received an intracutaneous injection of BCG vaccine, and 1,450 persons, comparable in age and sex, received an injection of sterile physiologic saline and served as controls.

The members of both groups ranged in age, at the beginning of the study, from less than one year to nineteen years. All were negative to both 0.00002 mg. and 0.005 mg. of purified protein derivative (PPD) (trichloracetic acid preparation) on their initial test preceding BCG vaccination or the injection of physiologic saline. As many persons of these two groups as could possibly be located were retested annually with 0.00002 mg. of PPD and, if negative forty-eight hours later, were retested with 0.005 mg. of PPD.

The injections and interpretations of the reactions were made with but few exceptions by the same personnel. These annual tuberculin tests were concomitant with annual roentgenographic examinations of the chest. The per cent of persons retested annually during

[1] From the Henry Phipps Institute, University of Pennsylvania, and the Branch of Health, Bureau of Indian Affairs, Department of the Interior, Washington, D. C.

the nine to eleven years of the study ranged from 70 to 96 per cent of those included in this study.

During one of the annual examination periods, an intracutaneous test with coccidioidin was performed simultaneously with the tuberculin test on some of the general population living on the Pima Agency, Arizona, and on all of the BCG-vaccinated persons and unvaccinated controls residing on the Pima Agency, Arizona; Wind River Agency, Wyoming; Turtle Mountain Agency, North Dakota; Rosebud Agency, South Dakota; and in southeastern Alaska.

The development of a definitive positive tuberculin reaction among the initially negative unvaccinated controls can be accepted as evidence of a natural infection with virulent tubercle bacilli. Among the BCG-vaccinated persons, however, the development of tuberculin hypersensitivity may be due either to the BCG vaccine, to natural infection with virulent tubercle bacilli, or to both. The course of tuberculin hypersensitivity has been followed in this study and in other epidemiologic studies of tuberculous infection both in the general population and among many thousands of BCG-vaccinated persons in different parts of the United States and Alaska. It has become evident from this experience that, in the vast majority of instances, the tuberculin reaction following BCG vaccination differs from that observed in the unvaccinated controls of the present study and from that of persons of the unvaccinated general population who have developed hypersensitivity due to natural tuberculous infection.

Among the originally negative unvaccinated persons of the present study who became tuberculin positive, as well as among persons of the general population who reacted to tuberculin, the level of tuberculin hypersensitivity was usually high, as indicated by a two-, three-, or four-plus reaction to either 0.01 mg. of Old Tuberculin or 0.00002 mg. of PPD. The local inflammatory reaction was conspicuous; the redness and, particularly, the edema were well defined, the latter being definitely palpable. In the center of edema an elevated, sharply defined area of induration was usually noted. In the more sensitive persons, lymphangitis, vesiculation, necrosis, or small petechial hemorrhages were occasionally noted. The area of induration was usually followed by a zone of deep pigmentation which persisted for several weeks or longer.

In this controlled study, it cannot be ignored that the same exposure to natural infection occurred among the vaccinated persons as among the control group. However, during the first year following vaccination, which was carried out only on tuberculin-negative persons, such exposure would be at a minimum. It has been assumed, therefore, that tuberculin hypersensitivity at the end of the first year among the 1,550 vaccinated Indians, with few exceptions, is the result of BCG vaccination. In this group, a total of 93.3 per cent of the persons vaccinated had become positive to PPD; 36.6 per cent to 0.00002 mg., and 56.7 per cent to the 0.005 mg. dose.

Aronson, Parr, and Saylor (5) have shown that the degree of tuberculin hypersensitivity was quantitatively and qualitatively less marked in BCG-vaccinated persons than in those developing hypersensitivity in the control group, as a result of natural infection with virulent tubercle bacilli. In general, in BCG-vaccinated persons, the local reaction to tuberculin was diffuse and less red than among the tuberculin-positive control group, and the edema was often slight and barely palpable. It is not meant to imply that the differences described divide one type of tuberculin reaction sharply from the other, since the range of the intensity of the inflammatory reaction resembles a spectrum and one type of reaction merges into the other.

The relationship of the tuberculin reaction to the occurrence of roentgenographically demonstrable pulmonary lesions was analyzed on the basis of the level of hypersensitivity

and the intensity of the local inflammatory reaction. The local reaction, which was read forty-eight hours after the injection of tuberculin PPD, was graded according to previously published standards (6).

Definite reactions to the initial dose of 0.00002 mg. of PPD in both groups have been interpreted as signifying a high level of hypersensitivity. With few exceptions, such reactions, once they appeared, were observed in subsequent re-tests. The level of hypersensitivity increased in some cases and decreased in others. Variations in the level of tuberculin hypersensitivity were divided into two groups. In one group were those who showed fluctuation in the degree of tuberculin sensitivity with the level changing from a reaction of 0.00002 to 0.005 and the reverse but at no time becoming negative. In the second group were persons in whom the positive reaction reverted to negative to 0.005 mg. of PPD and subsequently became positive. These fluctuations in tuberculin sensitivity have been reported previously (7).

OBSERVATIONS

Correlation of Tuberculin Reaction with Pulmonary Lesions

A correlation of the tuberculin reaction with roentgenographically demonstrable pulmonary lesions found among the unvaccinated control group and the BCG-vaccinated persons is presented in table 1.

It may be seen in table 1 that, among the controls, when the roentgenograms showed definite or suggestive evidence of tuberculosis (primary, minimal, or moderately advanced tuberculosis, pleural effusion, suspected primary or suspected reinfection-type tuberculosis), there was a conversion from an initial negative reaction of 0.005 mg. of PPD to a definite positive reaction to 0.00002 mg. of PPD in 66.6 to 85.1 per cent of the cases. This high level of hypersensitivity was maintained in these cases, with but few exceptions, throughout the period of the study.

In a small number of cases, tuberculin hypersensitivity increased, as shown by a rise in the per cent of those who reacted initially to 0.005 mg. of PPD and who subsequently reacted to 0.00002 mg. of PPD. In a small number of cases, the tuberculin reaction fluctuated from a high level of sensitivity to a low level and vice versa. In a few instances, tuberculin hypersensitivity reverted to negative or doubtful. This occurred most frequently in those whose roentgenograms showed calcified pulmonary nodules, and with but few exceptions such lesions occurred among the Pima Indians of Arizona, where Aronson, Saylor, and Parr (8) demonstrated a high incidence of coccidioidin sensitivity. The nontuberculous nature of a significant number of calcified pulmonary lesions is indicated by the fact that 26.8 per cent of persons with such lesions remained tuberculin negative during the course of the study dealing with the protective value of BCG vaccine, while 12.2 per cent showed a fluctuation in their tuberculin reaction from positive to negative or doubtful.

The validity of the diagnosis of nontuberculous pulmonary lesions in a high per cent of instances is indicated by the fact that in 43.2 per cent of these cases the tuberculin reaction remained negative. Among those whose roentgenograms failed to show any abnormal shadows and who were tuberculin tested, a total of 55.7 per cent remained tuberculin negative during the course of this study,

TABLE 1

THE RELATIONSHIP OF PULMONARY LESIONS TO THE TUBERCULIN TEST IN CONTROL AND BCG-VACCINATED PERSONS

CLASSIFICATION OF PULMONARY LESIONS	NUMBER	CONSISTENTLY POSITIVE TO 0.00002 MG.		INCREASING SENSITIVITY 0.005 MG. TO 0.00002 MG.		CONSISTENTLY POSITIVE TO 0.005 MG.		FLUCTUATING POSITIVE		FLUCTUATING POSITIVE WITH NEGATIVE OR DOUBTFUL		CONSISTENTLY NEGATIVE TO 0.005 MG.		NOT TESTED	
		Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Controls Reaction to 0.00002 or 0.005 mg. of PPD															
Primary	141	120	85.1	8	5.7	0	—	2	1.4	2	1.4	9	6.4	0	—
Minimal	31	26	84.0	2	6.4	0	—	0	—	1	3.2	2	6.4	0	—
Moderately advanced	20	14	70.0	3	15.0	1	5.0	0	—	0	—	1	5.0	1	5.0
Far advanced	3	1	33.3	0	—	0	—	0	—	0	—	0	—	2	66.6
Miliary	10	5	50.0	0	—	0	—	0	—	0	—	0	—	5	50.0
Pleural effusion	33	27	81.8	2	6.1	2	6.1	0	—	0	—	1	3.0	1	3.0
Calcified nodules	82	34	41.5	12	14.6	3	3.6	1	1.2	10	12.2	22	26.8	0	—
Suspected primary	27	18	66.6	1	3.7	1	3.7	1	3.7	0	—	6	22.2	0	—
Suspected reinfection	25	18	72.0	1	4.0	0	—	0	—	0	—	5	20.0	1	4.0
Nontuberculous	81	30	37.0	2	2.5	5	6.2	2	2.5	6	7.4	35	43.2	1	1.2
No lesion	997	277	27.8	23	2.3	53	5.3	71	7.1	0	—	555	55.7	18	1.8
Total	1,450	570	39.3	54	3.7	65	4.5	77	5.3	19	1.3	636	43.9	29	2.0
BCG-Vaccinated Reaction to 0.00002 or 0.005 mg. of PPD															
Primary	40	15	37.5	15	37.5	3	7.5	5	12.5	1	2.5	0	—	1	2.5
Minimal	11	7	63.6	2	18.2	0	—	1	9.1	1	9.1	0	—	0	—
Moderately advanced	2	1	50.0	1	50.0	0	—	0	—	0	—	0	—	0	—
Far advanced	1	0	—	1	100.0	0	—	0	—	0	—	0	—	0	—
Miliary	0	0	—	0	—	0	—	0	—	0	—	0	—	0	—
Pleural effusion	10	2	20.0	6	60.0	0	—	2	20.0	0	—	0	—	0	—
Calcified nodules	84	11	13.1	18	21.4	4	4.8	39	46.4	9	10.7	3	3.6	0	—
Suspected primary	16	3	18.8	8	50.0	1	6.2	4	25.0	0	—	0	—	0	—
Suspected reinfection	16	2	12.5	6	37.5	2	12.5	5	31.3	1	6.2	0	—	0	—
Nontuberculous	77	21	27.3	22	28.5	8	10.4	21	27.3	3	3.9	0	—	2	2.6
No lesion	1,283	407	31.7	342	26.6	226	17.7	226	17.7	47	3.6	26	2.0	9	0.7
Total	1,540	469	30.4	421	27.3	244	15.8	303	19.7	62	4.0	29	1.9	12	0.8

while 42.5 per cent had become positive to 0.00002 or 0.005 mg. of PPD. The number of cases of far advanced and miliary tuberculosis is so small that correlation with the tuberculin reaction would not be statistically significant.

The correlation of pulmonary lesions with tuberculin hypersensitivity in BCG-vaccinated persons is complicated by the fact that a positive tuberculin reaction may be the result of either the BCG vaccination, a superimposed tuberculous infection, or both. However, since hypersensitivity following BCG vaccination is usually of a low level, a definite increase in sensitivity may be interpreted as due to a superimposed infection with virulent tubercle bacilli.

It will be noted from table 1 that, among the vaccinated persons, a positive reaction to 0.00002 mg. of PPD was observed in a high per cent of those whose roentgenograms showed evidence of primary or minimal tuberculosis. The number of cases of moderately advanced and far advanced tuberculosis is too small to be significant statistically.

A positive reaction to 0.00002 mg of PPD was also observed among 27.3 per cent of those with nontuberculous pulmonary lesions and 31.7 per cent of those whose roentgenograms showed no abnormal shadows.

Effect of superimposed tuberculous infection in BCG-vaccinated persons: That a superimposed tuberculous infection in BCG-vaccinated persons increases tuberculin sensitivity is indicated by the observation that, in the vaccinated group, 27.3 per cent showed an increase of sensitivity from 0.005 mg. to 0.00002 mg. of PPD; while in the control group, only 3.7 per cent showed such an increase. This increase in tuberculin sensitivity among the vaccinated persons was most marked among those whose lesions were diagnosed as pleural effusion, suspected primary, suspected reinfection-type tuberculosis, or primary tuberculosis. A less marked increase in the per cent of persons whose tuberculin sensitivity increased was noted among those showing calcified pulmonary nodules and nontuberculous pulmonary lesions and those whose roentgenograms showed no abnormal shadows.

Among the BCG-vaccinated persons, the per cent who reacted consistently to 0.005 mg. of PPD or who showed fluctuation in the level of tuberculin sensitivity was significantly higher than that observed in the control group. The number who remained negative to 0.005 mg. of PPD during the study was only 1.9 per cent in the vaccinated group; while, in the control group, 43.9 per cent failed to react to the same dose of PPD at the end of the nine to eleven years of this study.

Fluctuation of tuberculin reaction: The small per cent of persons whose tuberculin reaction fluctuated from positive to negative and back occurred, with but few exceptions, among those living on the Pima Agency, Arizona. Although an increase in the level of tuberculin sensitivity among BCG-vaccinated persons with tuberculous or suspected tuberculous pulmonary lesions is shown in table 1, a more detailed analysis of the changes of the tuberculin reaction, by dose of tuberculin and by degree of reaction before and after the appearance of the pulmonary lesions, further supports this observation. Among the BCG-vaccinated persons, 93.3 per cent of those tested reacted to one or the other dose of PPD one year after vaccination. At that time the degree of reaction to PPD varied somewhat with different preparations of the vaccine but, in general, was of a low level of sensitivity. The degree of tuberculin reaction by dose of PPD

TABLE 2

Level of Tuberculin Sensitivity by Dose in BCG-Vaccinated Persons in Relation to Pulmonary Lesion

Pulmonary Lesion	Number	Reaction to Tuberculin	Reaction to 0.00002 mg. of PPD						Reaction to 0.005 mg. of PPD												Not Tested	
			1+		2+		3+		1+		2+		3+		Doubtful		Negative		Fluctuating			
			Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Primary	40	Initial*	4	10.3	8	20.6	3	7.7	3	7.7	15	38.4	1	2.5	2	5.1	3	7.7	0	—	1	2.5
		With lesion	2	5.1	13	33.4	17	43.7	2	5.1	4	10.2	1	2.5	0	—	0	—	0	—	1	2.5
Minimal	11	Initial*	2	18.2	4	36.4	3	27.2	0	—	2	18.2	0	—	0	—	0	—	0	—	0	—
		With lesion	0	—	4	36.4	7	63.6	0	—	0	—	0	—	0	—	0	—	0	—	0	—
Moderately advanced	2	Initial*	0	—	1	50.0	0	—	0	—	0	—	0	—	1	50.0	0	—	0	—	0	—
		With lesion	0	—	1	50.0	1	50.0	0	—	0	—	0	—	0	—	0	—	0	—	0	—
Far advanced	1	Initial*	0	—	0	—	0	—	0	—	1	100.0	0	—	0	—	0	—	0	—	0	—
		With lesion	0	—	0	—	1	100.0	0	—	0	—	0	—	0	—	0	—	0	—	0	—
Pleural effusion	10	Initial*	1	10.0	3	30.0	0	—	1	10.0	3	30.0	2	20.0	0	—	0	—	0	—	0	—
		With lesion	0	—	5	50.0	5	50.0	0	—	0	—	0	—	0	—	0	—	0	—	0	—
Calcified nodules	84	Initial*	15	19.5	15	19.5	5	6.5	0	—	25	32.5	11	14.3	0	—	6	7.7	0	—	7	8.3
		With lesion	2	2.4	26	30.9	17	20.2	0	—	11	13.1	0	—	0	—	3	3.6	25	29.8	0	—
Suspected primary	16	Initial*	2	12.5	3	18.8	1	6.2	1	6.2	7	43.8	1	6.2	1	6.2	0	—	0	—	0	—
		With lesion	1	6.2	7	43.8	4	25.1	0	—	1	6.2	0	—	1	6.2	0	—	2	12.5	0	—
Suspected reinfection	16	Initial*	5	31.3	2	12.5	0	—	2	12.5	6	37.5	0	—	1	6.2	0	—	0	—	0	—
		With lesion	3	18.7	6	37.5	3	18.8	0	—	3	18.8	1	6.2	0	—	0	—	0	—	0	—
Nontuberculous	77	Initial*	16	22.5	8	11.3	1	1.4	5	7.2	28	39.3	4	5.6	5	7.1	4	5.6	0	—	6	7.8
		With lesion	3	4.0	35	46.7	19	25.4	0	—	8	10.7	4	5.3	1	1.3	0	—	5	6.6	2	2.6
No lesion	1,283	Initial*	253	20.5	171	13.9	17	1.4	75	6.2	488	39.6	151	12.3	24	1.9	52	4.2	0	—	52	4.0
		Last test	105	8.2	548	43.1	187	14.7	13	1.0	179	14.1	54	4.2	5	0.4	37	2.9	146	11.4	9	0.7

* Tuberculin reaction one year after BCG vaccination.

one year after the administration of BCG vaccine is compared in table 2 with the degree of the tuberculin reaction observed in the presence of the different types of pulmonary lesions. For those with no demonstrable pulmonary lesions, the first post-vaccinal tuberculin test is compared with the last tuberculin test.

The data presented in table 2 indicate that one year following the administration of BCG vaccine a higher per cent of persons gave a definite reaction to 0.005 mg. of PPD or gave a one-plus reaction to 0.00002 mg. of PPD. The high tuberculin sensitivity observed among some of the vaccinated persons on their first post-vaccinal test may be due to a superimposed tuberculous infection which occurred during the first year following vaccination. Before or after the appearance of pulmonary lesions, a decrease was noted in the per cent of persons who had originally reacted to 0.005 mg. of PPD and an increase in the per cent of those who gave a marked reaction to 0.00002 mg. of PPD. This shift in the level of tuberculin sensitivity was most marked among those with primary or minimal tuberculosis or with pleural effusion. It is noteworthy that, among those with calcified pulmonary lesions, the shift in the intensity of tuberculin sensitivity was approximately the same as that noted among those with no abnormal pulmonary shadow.

Initial Appearance of Tuberculin Hypersensitivity in Relation to Initial Roentgenographic Abnormalities

Although it has been generally accepted that tuberculin hypersensitivity precedes roentgenographic appearance of tuberculous pulmonary lesions, data dealing with this phase of tuberculosis are scant. In a study of more than 2,000 infants from tuberculous homes in New York, in which the children were followed by roentgenographic examinations and tuberculin tests at intervals of three to six months, Levine (9) traced the evolution of a primary complex in 63 children less than one year of age. In 16 of these infants, roentgenographic evidence of involvement of the lung parenchyma preceded the appearance of tuberculin hypersensitivity.

In the present study, tuberculin tests and roentgenographic examinations were made at annual intervals, and the relationship between the appearance of the lesion and the development of tuberculin hypersensitivity on an annual basis can only be approximated. The time of appearance of the tuberculin reaction in the control group has been analyzed in relation to the time of appearance of the pulmonary lesions, and the findings are presented in table 3.

In the control group, the appearance of pulmonary lesions diagnosed as primary, moderately advanced tuberculosis, miliary tuberculosis, pleural effusion, suspected primary, or suspected reinfection-type tuberculosis was associated in a high per cent of cases with a high level of tuberculin hypersensitivity concomitant with the appearance of the lesion or with a positive tuberculin reaction one year preceding its appearance. On the other hand, the appearance of calcified pulmonary nodules or nontuberculous pulmonary lesions was associated with a significantly lower per cent of positive tuberculin reactions occurring at the time of, or one year preceding, the appearance of the lesion.

TABLE 3

TIME OF APPEARANCE OF TUBERCULIN SENSITIVITY IN RELATION TO PULMONARY LESIONS AMONG NONVACCINATED PERSONS

OCCURRENCE OF TUBERCULIN REACTION	PRIMARY		MINIMAL		MODERATELY ADVANCED		FAR ADVANCED		MILIARY		PLEURAL EFFUSION		CALCIFICATION		SUSPECTED PRIMARY		SUSPECTED REINFECTION		NONTUBERCULOUS		NEGATIVE	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Concomitant with lesion	88	62.4	13	41.9	9	45.0	1	33.3	4	40.0	19	57.6	6	7.3	12	44.4	8	32.0	15	18.5	0	—
Positive one year prior to lesion	13	9.2	5	16.2	2	10.0	0	—	0	—	4	12.1	4	4.9	0	—	3	12.0	5	6.2	0	—
Positive 13 months or more prior to lesion	13	9.6	10	32.2	2	10.0	0	—	0	—	6	18.1	25	30.5	6	22.2	5	20.0	8	9.9	0	—
Negative at time of lesion, positive one year later	8	5.8	0	—	0	—	0	—	1	10.0	1	3.3	7	8.5	0	—	0	—	6	7.4	0	—
Negative at time of lesion, positive 13 months later	10	7.1	0	—	0	—	0	—	0	—	0	—	15	18.3	3	11.1	1	4.0	10	12.3	0	—
Negative at time of lesion and subsequently	7	4.9	2	6.4	0	—	0	—	3	30.0	1	3.3	23	28.0	5	18.5	5	20.0	31	38.3	0	—
Negative year of lesion; positive before and after appearance of lesion	0	—	1	3.2	0	—	0	—	0	—	0	—	1	1.2	0	—	0	—	0	—	0	—
Positive reaction, no pulmonary lesion demonstrable	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—	424	43.3
Negative reaction, no pulmonary lesion demonstrable	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—	555	56.7
Not tested in year of lesion, positive one year later	2	1.4	0	—	3	15.0	2	66.2	2	20.0	1	3.3	0	—	1	3.7	3	12.0	4	4.9	0	—
Not tested in year of lesion, previously positive	0	—	0	—	4	20.0	0	—	0	—	1	3.3	1	1.2	0	—	0	—	2	2.5	0	—
Total	141		31		20		3		10		33		82		27		25		81		979	

In a significant per cent of cases of minimal tuberculosis, calcified pulmonary nodules, suspected primary, and suspected reinfection-type tuberculosis, the tuberculin reaction preceded the roentgenographic appearance of both tuberculous and nontuberculous lesions by two years or longer.

The appearance of pulmonary lesions several years after the appearance of a positive tuberculin reaction may be unrelated, since the appearance of the initial positive reaction may be the result of a tuberculous infection with no roentgenographically demonstrable pulmonary lesion or of a tuberculous infection occurring subsequently to the appearance of an initial nontuberculous pulmonary lesion. The basis for the former explanation is the observation that 43.3 per cent of the control group developed a definite tuberculin reaction, but at no time did these tuberculin-positive persons show any abnormal pulmonary shadows. The nontuberculous nature of many calcified pulmonary nodules, lesions of suspected primary and suspected reinfection-type tuberculosis, as well as lesions diagnosed as nontuberculous, is indicated by the behavior of the tuberculin reaction. A high per cent of the patients with such lesions failed to react to the intracutaneous injection of 0.00002 and 0.005 mg. of PPD concomitant with the appearance of the pulmonary lesions, or failed to react to tuberculin one year prior to or one year after the appearance of the lesion, or remained tuberculin negative during the course of the study.

The correlation of tuberculin reaction with the time of appearance of pulmonary lesions among the BCG-vaccinated persons is partially masked by the tuberculin hypersensitivity which follows BCG vaccination. However, with an awareness of this qualification, the relationship of the tuberculin reaction to the occurrence of pulmonary lesions among the BCG-vaccinated persons of this study is presented in table 4.

It will be noted in table 4 that a high per cent of cases of primary tuberculosis and suspected reinfection-type tuberculosis were associated with a positive tuberculin reaction concomitant with the appearance of the pulmonary lesions. Of the 18 cases of primary tuberculosis, 10 were associated with an increase in the post-vaccinal tuberculin reaction as indicated by a two-plus or three-plus reaction to 0.00002 mg. of PPD. In the 6 cases of suspected reinfection-type tuberculosis, there was no increase in the level of the post-vaccinal tuberculin hypersensitivity. Of the 14 patients with calcified pulmonary nodules associated with a concomitant tuberculin reaction, only 3 showed a high level of hypersensitivity, while the remaining 11 showed a low level of hypersensitivity. The one person with pleural effusion and 2 of the 3 persons with suspected primary tuberculosis showed a low level of tuberculin hypersensitivity, while the third person with suspected primary tuberculosis showed an increased hypersensitivity to tuberculin PPD. Of the 13 persons with nontuberculous pulmonary lesions, only 2 showed an increase in their tuberculin hypersensitivity.

A high per cent of roentgenographically demonstrable pulmonary lesions were preceded by a positive tuberculin reaction one or more years before the appearance of the lesion. In the vast majority of cases, the level of tuberculin hypersensitivity increased from a positive reaction to 0.005 mg. of PPD to a positive

TABLE 4

TIME OF APPEARANCE OF TUBERCULIN SENSITIVITY IN RELATION TO PULMONARY LESIONS AMONG BCG-VACCINATED PERSONS

OCCURRENCE OF TUBERCULIN REACTION	PRIMARY		MINIMAL		MODERATE		FAR ADVANCED		MILIARY		PLEURAL EFFUSION		CALCIFICATION		SUSPECTED PRIMARY		SUSPECTED REINFECTION		NONTUBERCULOUS		NEGATIVE	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Concomitant with lesion	18	45.0	1	9.1	0	—	0	—	0	—	1	10.0	14	16.6	3	18.7	6	37.5	13	16.9	0	—
Positive one year prior to lesion	7	17.5	0	—	0	—	0	—	0	—	1	10.0	4	4.8	3	18.7	3	18.7	15	19.5	0	—
Positive 13 months or more prior to lesion	7	17.5	7	63.7	1	50.0	1	100.0	0	—	5	50.0	23	27.5	7	43.8	5	31.2	33	42.9	0	—
Negative at time of lesion, positive one year later	4	10.0	1	9.1	0	—	0	—	0	—	2	20.0	30	35.6	2	12.5	1	6.3	6	9.1	0	—
Negative at time of lesion, positive 13 months or more	0	—	0	—	0	—	0	—	0	—	0	—	7	8.4	1	6.3	0	—	4	5.3	0	—
Negative at time of lesion and subsequently	0	—	0	—	0	—	0	—	0	—	0	—	3	3.5	0	—	0	—	2	2.7	0	—
Negative year of lesion, positive before and after appearance of lesion	1	2.5	0	—	0	—	0	—	0	—	0	—	1	1.2	0	—	0	—	2	2.7	0	—
Positive reaction, no pulmonary lesion demonstrable	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—	1,251	97.4
Negative reaction, no pulmonary lesion demonstrable	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—	33	2.6
Not tested in year of lesion, positive one year later	1	2.5	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—
Not tested in year of lesion, previously positive	1	2.5	2	18.1	1	50.0	0	—	0	—	1	10.0	2	2.4	0	—	1	6.3	3	3.9	0	—
Not tested year of lesion, previously negative	1	2.5	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—
Total	40		11		2		1		0		10		84		16		16		77		1,284	

reaction to 0.00002 mg. of PPD. This was conspicuously so among those diagnosed as primary, minimal tuberculosis, or suspected primary tuberculosis. On the other hand, among the 6 cases of pleural effusion, an increase of tuberculin hypersensitivity was noted in 2 cases one year after the appearance of the lesion; while, in the remaining 4 cases, increased tuberculin hypersensitivity preceded the pleural effusion. Of the 27 persons with calcified pulmonary nodules with a tuberculin reaction preceding the appearance of the lesion, 13 showed an increased tuberculin hypersensitivity before calcified nodules were seen, and in 14 there was no change in the level of the post-vaccinal tuberculin reaction. Of these 14 persons, 12 were from the Pima Agency, Arizona, an area of endemic coccidioidomycosis. Suspected reinfection-type tuberculosis with a positive tuberculin reaction preceding the appearance of the lesion was noted in 8 persons; of these, 6 showed no increase in the level of tuberculin hypersensitivity when the lesion was first recognized, while 2 experienced a definite increase in tuberculin hypersensitivity. Of the 48 persons with nontuberculous lesions with a positive tuberculin reaction, 18 showed a high level of hypersensitivity preceding the appearance of the lesion and the remaining 30 developed no change in the level of the post-vaccinal tuberculin reaction.

With the exception of those showing calcified pulmonary lesions, only a small per cent of persons with roentgenographically demonstrable pulmonary lesions were tuberculin negative at the time when the pulmonary lesion appeared, and subsequently became tuberculin positive. Of the 4 persons with primary tuberculosis in whom the lesion preceded the appearance of the tuberculin reaction, one showed a fluctuating type of tuberculin reaction and 3 had tuberculin reactions which resembled that noted following BCG vaccination. The one person with minimal tuberculosis and the 2 with pleural effusion showed a high level of tuberculin hypersensitivity within one year after the appearance of the pulmonary lesion. Calcified pulmonary nodules associated with a negative tuberculin reaction were found in 37 cases. A high level of tuberculin hypersensitivity was subsequently observed in 3 instances, while in the remaining 34 cases the level of hypersensitivity was that usually observed following BCG vaccination uncomplicated by a superimposed tuberculous infection. Of the 3 cases of suspected primary tuberculosis, 2 were followed by a high level of tuberculin hypersensitivity subsequent to the appearance of the pulmonary lesion, as was one case of suspected reinfection-type tuberculosis. In 10 cases of nontuberculous pulmonary lesions, the tuberculin reaction was negative at the time the lesion was detected, but subsequently the tuberculin reaction became positive. In these cases the tuberculin reaction resembled that noted following BCG vaccination.

DISCUSSION

The incidence of pulmonary lesions of both tuberculous and nontuberculous nature was determined among the BCG-vaccinated persons and unvaccinated control persons by the interpretation of serial roentgenograms made at approximately annual intervals during a period of nine to eleven years. Realizing the limitations in the use of objective roentgenographic interpretations alone for the

diagnosis of pulmonary lesions, it was further considered advisable to define the value of BCG vaccination in the control of tuberculosis by determining the relationship of the tuberculin reaction to different types of pulmonary lesions among BCG-vaccinated persons and control persons.

Analysis of the collected data indicates that, among the control persons, in most instances, the appearance of a pulmonary lesion diagnosed as tuberculous or suspect tuberculous was associated with a conversion of a negative tuberculin reaction to a positive reaction. Among the vaccinated persons, the occurrence of a tuberculous pulmonary lesion was expressed generally by a sharp increase in the level of hypersensitivity. In a small per cent of cases, the lesions diagnosed as tuberculous or suspected tuberculous were not associated with either a positive tuberculin reaction or an increase in tuberculin sensitivity. These cases may have represented nontuberculous lesions which roentgenographically mimicked tuberculous lesions or lesions of tuberculous etiology in anergic persons. In view of the facts that anergy is uncommon and that the development of tuberculin hypersensitivity following BCG vaccination discounts its presence, the present writers are inclined to consider that the absence of a definite tuberculin reaction in the presence of a lesion diagnosed as tuberculous strongly suggests that the lesion is of a nontuberculous nature.

This study also indicates the important role played by the tuberculin test in differentiating the etiology of calcified pulmonary lesions.

Although a definite positive tuberculin reaction occurs in the vast majority of persons with pulmonary lesions diagnosed as tuberculous, a significant per cent of persons react to tuberculin but fail to show any abnormal shadow of the chest. This evidence emphasizes the importance of the roentgenogram in selecting patients for hospitalization and treatment as well as the associated use of the tuberculin test in confirming the etiology of the disease. For epidemiologic purposes, roentgenographic surveys are inadequate and the tuberculin test is essential.

SUMMARY

The accuracy of interpretation of chest roentgenograms of 1,540 BCG-vaccinated persons and 1,450 unvaccinated control persons obtained at approximately annual intervals during a period of nine to eleven years was evaluated on the basis of the relationship of the time of appearance and degree of tuberculin sensitivity to the occurrence of the pulmonary lesions.

In the control group, the occurrence of pulmonary lesions diagnosed as tuberculous was usually associated with a conversion of the original negative tuberculin reaction to positive, either concomitantly with the appearance of the lesion, shortly before, or shortly thereafter.

Persons with pulmonary lesions diagnosed as nontuberculous, as well as persons with calcified pulmonary nodules, showed a significantly lower incidence of tuberculin conversions, which was somewhat higher than that observed among those with no pulmonary lesions.

Among the control persons who failed to show any abnormal pulmonary shad-

ows, 43.3 per cent became tuberculin positive during the course of the study, a per cent approximating that observed among those with nontuberculous lesions.

Among the BCG-vaccinated persons, the occurrence of tuberculous pulmonary lesions was associated in most instances with an increase in the level of the original post-vaccinal tuberculin sensitivity. As among the control persons, this increase was less marked among those diagnosed as showing nontuberculous lesions or calcified pulmonary lesions.

Among the vaccinated persons who showed no lesions, the increase in level of sensitivity approximated that observed among those with nontuberculous pulmonary lesions or calcified pulmonary nodules.

SUMARIO

La Correlación de la Reacción Tuberculínica con las Lesiones Pulmonares Descubribles Roentgenológicamente en los Vacunados con BCG y los Testigos

La exactitud de la interpretación de las radiografías torácicas de 1,540 personas vacunadas con BCG y 1,450 testigos no vacunados, tomadas a plazos aproximadamente anuales durante un período de nueve a once años, fué justipreciada a base de la relación de la fecha de la aparición e intensidad de la sensibilidad a la tuberculina con la ocurrencia de las lesiones pulmonares. Entre los testigos, la ocurrencia de las lesiones pulmonares diagnosticadas como tuberculosas se asoció por lo general con un viraje de la primitiva reacción tuberculínica negativa a positiva, ya junto con la aparición de la lesión, o poco antes o poco después. Las personas que tenían lesiones pulmonares diagnosticadas como no tuberculosas, así como las que tenían nódulos pulmonares calcificados, revelaron una incidencia significativamente menor de virajes de las reacciones tuberculínicas, que era algo mayor que la observada entre las que no tenían lesiones pulmonares. Entre los testigos que no revelaron sombras pulmonares anormales, 43.5 por ciento se volvieron tuberculino-positivos durante el estudio, porcentaje ese que se aproximaba al observado entre los que tenían lesiones no tuberculosas. Entre los becegetizados, la existencia de lesiones pulmonares tuberculosas se asoció en la mayor parte de los casos con un aumento de la intensidad de la primitiva sensibilidad postvacunal a la tuberculina. Lo mismo que entre los testigos, ese aumento fué menos notable entre aquéllos en que se diagnosticaron lesiones no tuberculosas o lesiones pulmonares calcificadas. Entre los vacunados que no mostraron lesiones el aumento de la sensibilidad se aproximaba al observado entre los que tenían lesiones pulmonares no tuberculosas o nódulos pulmonares calcificados.

RESUME

La corrélation de la réaction à la tuberculine et des lésions pulmonaires démontrables radiologiquement chez les sujets vaccinés par le BCG et les sujets-témoins

Il a été procédé à une évaluation de la précision de l'interprétation de radiogrammes du poumon chez 1540 sujets vaccinés par le BCG et 1450 témoins non-vaccinés, les clichés étant pris à intervalles d'un an environ pendant des périodes variant de un à onze ans. Les auteurs ont pris pour base la relation entre le moment de l'apparition et le degré de la sensibilité à la tuberculine et la manifestation des lésions tuberculeuses pulmonaires. Parmi les sujets témoins, l'apparition de lésions pulmonaires diagnostiquées tuberculeuses s'accompagnait habituellement d'une conversion de la tuberculino-réaction initiale négative en réaction positive, celle-ci se produisant, soit peu avant soit peu après l'apparition de la de la lésion du poumon. Chez les sujets affectés de lésions pulmonaires diagnostiquées non-tuberculeuses, de même que chez les individus atteints de nodules pulmonaires primaires calcifiés, on observait une moindre fréquence de la conversion des réactions à la tuberculine, bien que cette fréquence se soit montrée légèrement plus élevée que celle observée

dans le groupe indemne de tuberculose. Parmi les sujets-témoins ne présentant pas d'opacités pulmonaires anormales, la réaction est devenue positive chez 43% d'entre eux au cours de l'étude. Cette proportion est sensiblement la même que celle observée dans le groupe indemne de lésions tuberculeuses. Parmi les sujets vaccinés par le BCG, l'apparition des lésions pulmonaires tuberculeuses étaient, dans la plupart des cas, associées à un accroissement du degré de la tuberculino-sensibilité post-vaccinale originale. De même que pour les sujets-témoins, cet accroissement était moins marqué parmi les sujets porteurs de lésions diagnostiquées non-tuberculeuses ou présentant des lésions pulmonaires calcifiées. Parmi les sujets vaccinés ne présentant aucune lésion, l'accroissement du degré de la sensibilité se rapprochait de celui qui était observé parmi les cas affectés de lésions pulmonaires non-tuberculeuses ou de nodules primaires calcifiés.

REFERENCES

(1) Stein, S. C., and Aronson, J. D.: The occurrence of pulmonary lesions in BCG-vaccinated and unvaccinated persons, Am. Rev. Tuberc., 1953, *68*, 695.

(2) Yerushalmy, J., Harkness, J. T., Cope, J. H., and Kennedy, B. R.: The role of dual reading in mass radiography, Am. Rev. Tuberc., 1950, *61*, 443.

(3) Garland, L. H., and Cochrane, A. L.: Results of an international test in chest roentgenogram interpretation, J.A.M.A., 1952, *149*, 631.

(4) Groth-Petersen, E., Løvgreen, A., and Thillemann, J.: On the reliability of the reading of photofluorograms and the value of dual reading, Acta tuberc. Scandinav., 1952, *26*, 13.

(5) Aronson, J. D., Parr, I., and Saylor, R. M.: The specificity and sensitivity of the tuberculin reaction following vaccination with BCG, Am. J. Hyg., 1941, *33*, 42.

(6) Aronson, J. D.: The purified protein derivative, with special reference to the technique of tuberculin injections and the grading of reactions, Am. Rev. Tuberc., Supplement, 1934, *30*, 727.

(7) Aronson, J. D.: The fluctuation of the tuberculin reaction in different geographic areas and its relationship to resistance, Am. Rev. Tuberc., 1951, *63*, 121.

(8) Aronson, J. D., Parr, I., and Saylor, R. M.: Relationship of coccidioidomycosis to calcified pulmonary nodules, Arch. Path., 1942, *34*, 31.

(9) Levine, M. I.: Sequence of roentgen evidence of tuberculosis and cutaneous sensitivity to tuberculin, Am. J. Dis. Child., 1939, *59*, 799.

CULTURAL PROPERTIES OF M. TUBERCULOSIS IN RESECTED PULMONARY LESIONS OF PATIENTS TREATED WITH STREPTOMYCIN AND PARA-AMINOSALICYLIC ACID[1]

GEORGE E. GRANVILLE, DANIEL E. JENKINS, DENTON A. COOLEY, MICHAEL E. DEBAKEY, FRANCES C. WHITCOMB, AND BÉLA HALPERT

(Received for publication July 6, 1953)

INTRODUCTION

The introduction of long-term antimicrobial therapy for the treatment of tuberculosis has stimulated inquiry into the role that such therapy may play in rendering *Mycobacterium tuberculosis* dormant or nonviable within the tissues of the host. It appears now that the effect on the microorganism is partly direct and partly mediated through other factors within the tissues of the host (1, 2, 3). Whether the organisms subjected to these effects are dead or have been rendered dormant and nonculturable has not as yet been fully evaluated (4, 5, 6, 7). Improved surgical approaches have afforded opportunities to investigate the presence and behavior of *M. tuberculosis* from lesions in different phases of healing and after varying periods of drug therapy (8). The present study was undertaken to inquire further into the cultural properties of *M. tuberculosis* from resected pulmonary lesions.

MATERIALS AND METHODS

Clinical Material

Segments or portions of lung tissue were removed surgically, subsequent to April, 1951, from 21 patients who received streptomycin and para-aminosalicylic acid (PAS) therapy for pulmonary tuberculosis. The tissues so obtained were studied for the presence and cultural properties of *M. tuberculosis* by bacteriologic and pathologic methods.

All of the patients (18 white, 3 Negro) were males, 18 of them in the third and fourth decades of life. The youngest patient was twenty-three; and the oldest, fifty-five. At the time of admission to the hospital, the extent of the pulmonary lesions was minimal in one patient, moderately advanced in 7, and far advanced in 13. At the time of operation the pulmonary lesions in all patients were, as viewed on monthly roentgenograms of the chest, either stable or very slowly regressive. Sputum or gastric cultures for *M. tuberculosis* were positive at this hospital in all but 2 of the patients and, in these, positive cultures had previously been obtained in other hospital laboratories. One or more positive cultures of sputum or gastric content were obtained within a ninety-day period prior to operation in 10 patients; cultures were consistently negative for *M. tuberculosis* for at least ninety days prior to operation in all of the remaining 11 patients.

Streptomycin, alone or in combination with PAS, had been administered to 11 patients prior to admission to this hospital; therefore, the course of drug therapy given before opera-

[1] From the Departments of Medicine, Surgery, and Pathology, Baylor University College of Medicine; and the Veterans Administration Hospital, Houston, Texas.

tion was considered as re-treatment. The remaining 10 patients received one continuous course of streptomycin and PAS therapy for the first time. Seventeen patients received streptomycin and PAS continuously for at least four months prior to operation; the remaining 4 patients had three weeks, three weeks, one month, and two and one-half months of drug therapy, respectively. The regimen of drug therapy in all patients included PAS, 12 gm. daily. In addition, 15 patients received streptomycin, 1 gm. daily; 3 patients, streptomycin, 1 gm. three times weekly; 2 patients, streptomycin, 1 gm. twice weekly; and one patient, streptomycin, 0.5 gm. daily.

All of the patients were on bed rest during the period of streptomycin and PAS therapy. Six of them received pneumoperitoneum and one patient received pneumothorax.

Method of Study of Resected Specimen

The surgically removed portion of lung was immediately delivered to the laboratory in a sterile container. After orientation of the location of the centers of involvement on the roentgenogram, the specimen was bisected with a sharp large knife directed toward the lesions. To decrease contamination from one area to another, a guillotine cut was made rather than a drawing stroke. From all areas of cavitation and from large areas of caseation, material was obtained with sterile swabs for direct smear and culture. Tissue from these areas of cavitation or caseation was then removed, macerated with sterile sand, digested with 3 per cent sodium hydroxide, smeared, and planted for culture on one tube each of four different media: ATS medium, Löwenstein-Jensen, Herrold's egg-yolk agar, and 25 per cent blood-bank agar. In addition, direct susceptibility studies for streptomycin were initiated, using ATS medium, containing 3, 10, and 100 γ of streptomycin per ml. The organism was considered resistant to streptomycin when growth in the 10 γ tube was equivalent to, or greater than, growth in the control tube. All tubes showing no growth were incubated at 37° C. for a period of twelve weeks before they were discarded.

After the material was obtained for bacteriologic study, the specimen was fixed in 10 per cent formalin, photographed, and representative portions of the walls of the cavities or of the solid lesions, as well as from other areas, were taken for microscopic study. In addition to routine paraffin sections stained with hematoxylin and eosin, several additional microscopic slides were stained with an acid-fast stain. In order to secure reliance on the results, suitable control slides were stained simultaneously, and several sets of acid-fast stained slides were prepared from each block of tissue.

RESULTS

The lesions from patients with open cavities (table 1) yielded positive smears for *M. tuberculosis* in all of the 9 patients. Cultures for *M. tuberculosis* from the same lesions were positive in 5 of the 9 patients. Drug-susceptibility studies disclosed that the organisms cultured were streptomycin-susceptible in 4 and streptomycin-dependent in one of these patients.

The morphologic changes in the lesions of the lungs in the 9 patients with open cavities were interpreted as fibrocaseous, with the caseous component predominating. The cavity in each instance was lined by a tuberculous granulation tissue covered with a zone of caseous material. Around the cavity there was a fibrous connective tissue zone of varying width delimiting, more or less completely, the area of involvement. Peripheral to the connective tissue zone were tubercles of various sizes. These had caseous or fibrocaseous centers with abundant palisading epithelioid cells and giant cells of the Langhans' type. Tubercles were observed in the mucosa of small bronchi and were scattered in the pulmonic tissue at some

distance from the area of cavitation. Intimal thickening, sometimes with narrowing or obliteration of the lumen, was often observed in blood vessels around the wall of the cavity. In 4 of the 9 patients, bronchial lumina adjacent or continuous with the cavity were lined by columnar cells which continued into squamous epithelium. In some cavities the squamous epithelium lined a part of the wall which was covered elsewhere by tuberculous granulation tissue (9). There was little, if any, increase of new fibrous connective tissue around the area of cavitation, nor was there any cellular reaction which might be interpreted as an attempt to further delimit the lesion.

TABLE 1

PATIENTS WITH OPEN CAVITIES

PATIENT	AGE	EXTENT OF DISEASE	STREPTOMYCIN AND PAS THERAPY			LAST CULTURE POSITIVE FOR M. TUBERCULOSIS	RESECTION	SPECIMEN	ORGANISMS IN:		
			Status	Dosage	Duration				Smears (Gaffky)	Cultures	Tissue Slides
					days						
S. A.	33	Far advanced	O	(1)	300	3/13/51	5/21/51	Lobe S-829-51	VI	+d	+
W. F.	27	Far advanced	R	(1)	300	10/12/51	10/29/51	Lung S-1762-51	VII	+s	+
F. L.	28	Far advanced	R	(1)	180	1/8/52	1/25/52	Lung S-139-52	VI	+s	+
H. Q.	55	Far advanced	R	(1)	21	4/3/52	4/18/52	Lobe and segment S-658-52	V	−	+
J. A.	30	Far advanced	O	(1)	380	11/5/51	5/16/52	Lobe S-439-52	VII	−	+
P. W.	52	Moderately advanced	O	(2)	420	3/18/52	5/21/52	Lobe S-880-52	V	−	−
H. H.	23	Far advanced	R	(3)	165	7/8/52	9/9/52	Lobe S-1487-52	VI	+s	−
R. C.	28	Far advanced	R	(3)	75	4/15/52	10/10/52	Lobe S-1658-52	VIII	−	−
T. S.	33	Far advanced	R	(3)	180	10/17/52	11/18/52	2 segments S-1875-52	IV	+s	−

O—Original; R—Re-treatment.
(1)—Streptomycin, 1 gm. per day and PAS, 12 gm. per day.
(2)—Streptomycin, 1 gm. twice weekly and PAS, 12 gm. per day.
(3)—Streptomycin, 1 gm. three times weekly and PAS, 12 gm. per day.
s—Streptomycin-susceptible; d—Streptomycin-dependent.

Acid-fast stains of the microscopic slides from the lung were positive for *M. tuberculosis* in 5 of the 9 patients with open cavities. The cultures were positive in only 3 of these 5 patients (table 1).

The lesions from patients with solid nodules in the lungs yielded positive smears for *M. tuberculosis* in 5 and negative smears in the remaining 7 patients (table 2). Cultures for *M. tuberculosis* from the same lesions were positive in 2 of the 5 patients whose smears were positive. The organism in one of these cultures was streptomycin-susceptible and in another, streptomycin-resistant.

The morphologic changes in the lesions of lungs from the 12 patients with solid lesions were also interpreted as fibrocaseous with abundant caseation in the cen-

ters of the lesions. Epithelioid cells and giant cells of the Langhans' type were numerous or few; and the delimiting fibrous connective tissue capsule about the caseous areas, narrow or broad. In most instances the lesions were nodular with several areas of involvement. In more than half of the lungs, there were abundant slitlike spaces in some of the caseous areas, deposits of deep blue-stained granules, and giant cells were few or absent. Around these lesions the fibrous connective

TABLE 2

PATIENTS WITH CLOSED LESIONS

PATIENT	AGE	EXTENT OF DISEASE	STREPTOMYCIN AND PAS THERAPY			LAST CULTURE POSITIVE FOR M. TUBERCULOSIS	RESECTION	SPECIMEN	ORGANISMS IN:		
			Status	Dosage	Duration				Smears (Gaffky)	Cultures	Tissue Slides
					days						
J. B.	36	Minimal	O	(1)	21	None	4/16/51	Wedge S-640-52	–	–	–
*W. T.	55	Far advanced	O	(1)	465	10/22/50	5/8/51	Lobe S-810-51	II	–	+
W. N.	28	Far advanced	R	(1)	420	3/13/50	5/10/51	2 lobes, S-754-51	–	–	+
*W. H.	31	Far advanced	O	(1)	345	9/10/50	7/2/51	Lobe and segment S-1065-51	–	–	–
*R. J.	37	Moderately advanced	O	(1)	405	6/21/51	7/5/51	Segment S-1075-51	VII	–	+
*J. C.	28	Moderately advanced	O	(1)	30	6/25/51	7/30/51	Segment S-1213-51	–	–	–
*C. P.	26	Moderately advanced	R	(1)	120	6/26/51	10/9/51	Segment S-1645-51	–	–	+
*J. M.	35	Moderately advanced	O	(1)	135	3/2/51	4/1/52	2 segments, S-542-52	VI	–	+
L. W.	28	Far advanced	R	(3)	210	5/7/52	6/24/52	3 wedges, S-1087-52	VIII	+r	+
*O. S.	39	Moderately advanced	O	(1)	225	12/12/51	7/15/52	Segment S-1196-52	III	+s	–
M. C.	39	Moderately advanced	R	(2)	165	1/14/52	9/9/52	Lobe S-1488-52	–	–	–
D. L.	27	Far advanced	R	(1)	120	None	9/19/51	Lobe and segment S-1537-51	–	–	+

* Patients with filled-in cavities.
O—Original; R—Re-treatment.
(1)—SM, 1 gm. per day and PAS, 12 gm. per day.
(2)—SM, 1 gm. twice weekly and PAS, 12 gm. per day.
(3)—SM, 0.5 gm. per day and PAS, 12 gm. per day.
r—Streptomycin-resistant; s—Streptomycin-susceptible.

tissue capsule was broad, dense, and hyalinized. Miliary and conglomerate tubercles were often observed in the nearby pulmonic tissue outside the capsules of the nodular lesions. In no instance was squamous epithelial lining observed, nor was any squamous epithelium seen in adjacent bronchiolar or bronchial lumina.

In 7 of the 12 patients with closed lesions, acid-fast stains of microscopic slides from the lungs were positive. Smears from the specimen of lung were positive for acid-fast bacilli in 4 of these 7 patients and cultures were positive for *M. tuberculosis* in only one.

COMMENT

The results of the present study do not reach the core of the problem and, as might be expected, do not provide the final answer to the question of whether the microorganisms presumably subjected to the effects of antimicrobial therapy in the patients studied were alive or dead.

It appears certain, however, that *M. tuberculosis* was not destroyed in the lesions of the patients with open cavities; the microorganism could be demonstrated by smear from the lesions in all, and could be recovered by culture in more than half of the patients. The tissue reaction was largely that of caseous necrosis with a zone of epithelioid cells and giant cells inside a band of connective tissue. This kind of granulation tissue is a specific response to *M. tuberculosis*. The production of new lesions is perhaps dependent on multiplication of the organisms. Thus, in patients with open cavities, the most that the antimicrobial therapy might be expected to accomplish is to hinder the multiplication of the *M. tuberculosis* and, thus, the spread of lesions. It appears that streptomycin and PAS did not fully accomplish either of these objectives in this group of patients. The progress of the disease seems to have been retarded, however, without an apparent surrounding tissue reaction to wall off or obliterate the lesion.

M. tuberculosis could be demonstrated by one of three methods, smear, culture, or tissue stain, in 8 of the 12 patients with closed lesions. In the content of some of these lesions, there was often evidence of beginning calcification and the capsules around these lesions were broad, dense, and hyalinizing, walling off the areas of caseation. Whether or not the organisms in these areas were still alive seems of little immediate consequence if their spread could have been prevented or blocked by the surrounding scar tissue. The presence of miliary and conglomerate tubercles outside the capsule of the nodular caseous lesions suggests that there were viable organisms in these lesions, although *M. tuberculosis* could be cultured from the closed lesions of only 2 of the patients.

SUMMARY

Morphologic and bacteriologic studies are presented of surgically removed portions of lung tissue from 21 patients who had received streptomycin and para-aminosalicylic acid (PAS) on various regimens continuously for periods of one to seventeen months before operation.

Among the 9 patients with open cavities, the lesions yielded positive smears for acid-fast bacilli in all, and cultures were positive for *M. tuberculosis* in 5. Acid-fast stains of microscopic slides were positive in 5 of the patients.

Among the 12 patients with closed lesions, acid-fast smears were positive in 5, and cultures were positive for *M. tuberculosis* in 2. Acid-fast stains of microscopic slides were positive in 7 of the patients.

Acid-fast organisms were thus demonstrated by at least one of the three methods, smear, culture, or tissue stain, in 17 of the 21 patients.

It is concluded that *M. tuberculosis* is not destroyed by streptomycin and PAS in patients with open cavities. In those with closed lesions, morphologic evidence

suggested that the organisms were still alive although they could be cultured in only 2 of the patients.

SUMARIO

Propiedades Culturales del M. Tuberculosis en las Lesiones Pulmonares Resecadas de Enfermos Tratados con Estreptomicina y Acido Para-Aminosalicílico

Preséntanse estudios morfológicos y bacteriológicos de porciones de tejido pulmonar extirpadas quirúrgicamente a 21 enfermos que habían recibido estreptomicina y ácido para-aminosalicílico (PAS) con varios regímenes continuamente durante períodos de tiempo que comprendieron de uno a diecisiete meses antes de la operación.

De los 9 enfermos con cavernas abiertas, las lesiones rindieron en todos frotes positivos para el *M. tuberculosis* y los cultivos fueron positivos en 5. La coloración ácidorresistente de las laminillas microscópicas fué positiva para el *M. tuberculosis* en 5 de los enfermos.

De los 12 enfermos que tenían lesiones cerradas, en 5 fueron "positivos" los frotes y en 2 los cultivos. En 7 de los sujetos, resultó "positiva" la coloración ácidorresistente de las laminillas microscópicas.

Se descubrieron, pues, bacilos ácidorresistentes en 17 de los 21 enfermos por uno a lo menos de los tres métodos, frote, cultivo o tinción histológica.

Dedúcese que el *M. tuberculosis* no es destruído por la estreptomicina y el PAS en los enfermos que tienen cavernas abiertas. En los de lesiones cerradas, los datos morfológicos sugerían que los microbios estaban todavía vivos, aunque no pudieron cultivarse más que en 2 de los pacientes.

RESUME

Propriétés culturales du M. tuberculosis de lésions pulmonaires réséquées chez des malades traités par la streptomycine et l'acide para-aminosalicylique

Présentation d'études morphologiques et bactériologiques effectuées sur des fragments de tissu pulmonaire provenant de résections pratiquées chez 21 tuberculeux ayant reçu un traitement continu de streptomycine-PAS pendant des périodes de un à dix-sept mois avant l'intervention.

Parmi les 9 malades présentant des lésions cavitaires ouvertes, les lésions ont donné des étalements positifs pour le *M. tuberculosis* chez tous les malades; les cultures furent positives chez 5 d'entre eux. L'examen microscopiques des lames après coloration des microorganismes acido-resistants a été "positif" chez 5 d'entre eux.

Parmi les douze malades porteurs de lésions fermées, les étalements furent "positifs" chez 5 et les cultures "positives" chez 2 d'entre eux. L'examen microscopique des lames après coloration des microorganismes acido-résistants fut positif chez 7 des malades.

La présence de microorganismes acido-résistants a été ainsi démontrée chez 17 des 21 malades par l'une au moins des trois méthodes: étalement, culture ou coloration des tissus.

Conclusion: le *M. tuberculosis* n'est pas détruit par la streptomycine et le PAS chez les tuberculeux porteurs de lésions cavitaires ouvertes. Chez ceux dont les lésions étaient fermées, des signes morphologiques suggéraient la présence de bacilles encore vivants, bien qu'ils n'aient pu être décelés par culture que chez 2 des malades.

REFERENCES

(1) DUBOS, R. J.: Chemical factors affecting the survival and multiplication of tubercle bacilli *in vivo*, Tr. of the Eleventh Conference on the chemotherapy of tuberculosis, Veterans Administration, Army, Navy, January, 1952, p. 234.

(2) DUBOS, R. J.: Discussion on treatment of tuberculous meningitis and survival of bacilli in tuberculous lesions, Am. Rev. Tuberc., 1952, *65*, 637.

(3) CANETTI, G.: Le Bacille de Koch. Dans la Lesion Tuberculeuse du Poumon, Editions Medicales Flammarion, France, 1946, p. 82.

(4) D'Esopo, N., Bernstein, S., Lee, W. F., Decker, A. M., and Steenken, W., Jr.: The bacteriology of resected lesions during chemotherapy, Tr. of the Eleventh Conference on the chemotherapy of tuberculosis, Veterans Administration, Army, Navy, January, 1952, p. 230.

(5) Beck, F., and Yegian, D.: A study of tubercle bacilli in resected pulmonary lesions, Am. Rev. Tuberc., 1952, *66:* 44.

(6) Medlar, E. M., Bernstein, S., and Steward, D. M.: A bacteriologic study of resected tuberculous lesions, Am. Rev. Tuberc., 1952, *66*, 36.

(7) Yegian, D.: Biology of tubercle bacilli in necrotic lesions, Am. Rev. Tuberc., 1952, *66*, 629.

(8) Ryan, B. J., Medlar, E. M., and Welles, E. S.: Simple excision in the treatment of pulmonary tuberculosis, J. Thoracic Surg., 1952, *23*, 327.

(9) Auerbach, O., Katz, H. L., and Small, M. J.: The effect of streptomycin therapy on the bronchocavitary junction and its relation to cavitary healing, Am. Rev. Tuberc., 1953, *67*, 173.

SUSCEPTIBILITY TO ISONIAZID AND PATHOGENICITY OF TUBERCLE BACILLI[1]

HUBERT BLOCH, DANIEL WIDELOCK, AND LENORE R. PEIZER

(Received for publication June 2, 1953)

INTRODUCTION

It has been asserted that tubercle bacilli which have acquired resistance against isoniazid are less virulent than their parent strain (1). The implications that such observations carry for the management of patients are obvious because a large proportion of tuberculous patients develop drug-resistant strains and do not become sputum "negative." It is important to know whether it is justified to regard such patients as less hazardous for their environment than those who disseminate non-drug-resistant bacteria.

The Department of Health of the City of New York conducted a study on 90 patients who received isoniazid during an observation period of twenty-six weeks. None of these patients was known to have had isoniazid treatment before the present study, and most of them had tubercle bacilli showing high drug susceptibility before the treatment started. In the course of this study, some patients showed marked clinical improvement, others remained unchanged, and some worsened. In all three categories, there were some who continued to have positive sputum which contained drug-resistant tubercle bacilli. The degree of resistance of the organisms isolated from this sputum ranged from bacteria which were inhibited by 0.1 γ of isoniazid per ml. of medium to organisms which grew in the presence of up to 50.0 γ per ml. of the drug. The virulence for mice of 20 of these cultures of tubercle bacilli was tested to see whether there was any correlation between the degree of virulence and the degree of drug resistance, on one hand, and between virulence and the clinical state of the patients from whom the bacteria were obtained, on the other hand. The twenty strains were selected for this study as a representative cross-section of the entire range of drug resistance.

METHODS

Primary isolation of cultures: Twenty-four-hour samples of sputum were homogenized and concentrated in the usual way with sodium hydroxide and aliquot amounts of the concentrates inoculated on Löwenstein, Jensen, and Peizer-Schechter media (2). The cultures were incubated for approximately four weeks and then stored at 4° C. until they were used for animal experiments. The drug susceptibility of the isolated strains was tested at the time of their primary isolation, but the strains were re-tested before being used for animal inoculation, as described below.

Determination of drug susceptibility: Löwenstein and Peizer-Schechter media with isoniazid were inoculated with bacteria from one-week-old Tween-albumin cultures as used for

[1] From the Division of Applied Immunology, The Public Health Research Institute of The City of New York, Inc.; and the Bureau of Laboratories, Department of Health of The City of New York.

TABLE 1

RELATIONSHIP BETWEEN VIRULENCE AND DEGREE OF ISONIAZID RESISTANCE IN MICE

CULTURE NUMBER	DRUG RESISTANCE; IN VITRO GROWTH IN THE PRESENCE OF							GROSS RATING OF DRUG RESISTANCE	PATHOGENICITY FOR MICE	
	0.1	0.5	1.0	5.0	10.0	25.0	50.0		Days after Infection Individual Mice Died	Number of Mice Sacrificed after 54 Days
	*γ of isoniazid per ml.**									
5	++++	0	0	0	0	0	0		13, 18, 34, 42, 44, 52	4
7	++++	0	0	0	0	0	0		42, 53	8
1841	++++	0	0	0	0	0	0	0	13, 35, 34, 38, 40, 44, 53	3
213	+	0	0	+	0	0	0		20, 21, 21, 21, 30, 37, 38, 50, 50	1
069	++++	0	0	0	+	0	0		23, 27, 40, 44	6
1967	++	+	+	0	0	0	0		25, 27, 34, 53	6
2475	++++	++++	+++	0	0	0	0		34, 38, 42, 53	6
2258	+++	++++	+++	+	0	0	0	+	14, 17, 17, 18, 18, 18, 18, 18, 18, 44	0
2667	++++	++++	++	+	0	0	0		23, 24, 40, 50, 53	5
2111	+++	+	++	0	0	+	0		18, 18, 18, 19, 19, 19, 22, 23, 38	1
273	++++	++++	++++	++++	+	0	0		—	10
2926	++++	++++	++++	++++	+++	0	0		18, 19, 20, 21, 21, 23	4
2181	++++	++	++	++	++	+	0	++	23, 26, 33, 40, 52, 53	4
2216	++++	++++	++++	+++	+	+	0		13, 53	8
2297	+	+	+	++	+	+	+		19, 21, 22, 23, 23, 25, 29, 30, 53	1
173	++++	++	+	++	+	+	+		27, 27, 27	7
2829	++++	++++	++++	++++	++++	++++	+		19, 21, 21, 23	6
1035	+++	++	++	+	++	+	++	+++	24, 26, 35, 37, 42, 44, 53	3
60	+++	+++	+	+++	+	++	++		22, 23, 25, 25, 27, 28, 28	3
2308	++++	++++	++++	++++	++++	++++	++++		22	

* The symbols indicate the variations in growth intensity over a scale ranging from 0 to indicate no macroscopically visible colonies to ++++ for the most luxuriant type of growth.

animal infection (*see* below). The media contained the following amounts of isoniazid: 0.1, 0.5, 1.0, 5.0, 10.0, and 50.0 γ per ml. The degree of resistance was defined by determining the highest concentration of isoniazid in the presence of which growth occurred and by estimating the intensity of bacterial growth in the various dilutions of the isoniazid media.

Determination of virulence: The cultures were transferred from the solid media on which they had first been isolated into liquid Tween-albumin medium (3) containing 0.05 per cent Tween 80[2] and 0.5 per cent bovine albumin. After approximately ten days' incubation, they were re-transferred into another tube of the same medium, and eight-day cultures of the second transfer were used for animal inoculation. All cultures were adjusted to the same optical density corresponding to approximately 5×10^5 organisms per ml.

TABLE 2

CORRELATION BETWEEN CLINICAL DEVELOPMENT OF PATIENTS DURING ISONIAZID TREATMENT AND BACTERIAL VIRULENCE FOR MICE OF THE ISOLATED CULTURES

PATIENT	CULTURE NUMBER*	CLINICAL DEVELOPMENT OF THE PATIENT DURING ISONIAZID TREATMENT†	BACTERIAL DRUG RESISTANCE		BACTERIAL VIRULENCE	
			Initial	After 26 Weeks	Initial	After 26 Weeks
TM	69	Marked improvement	0		++	
	1841			0		+++
FM	7	Marked improvement	0		+	
	2731			++		+
AD	5	Marked improvement	0		+++	
	2475			+		++
JT	60	No change	+++		+++	
	1036			+++		+++
LM	173	Slight worsening	+++		++	
	2829			+++		++
AC	213	Moderate worsening	0		++++	
	2667			+		+++

* Compare table 1.

† This evaluation is based on roentgenographic findings.

Mice of the CF_1 strain[3] were infected intravenously with 0.1 ml. of these suspensions, each culture being tested on a group of 10 mice. At the same time, the drug resistance of the bacteria was tested by inoculating a set of isoniazid-containing tubes with 0.1 ml. of the same bacterial suspensions which served for the animal inoculation.

The virulence of the organisms was expressed by the time which elapsed between infection and death of the mice. All survivors were sacrificed and autopsied fifty-four days after infection. The chosen infective dose was a relatively weak one and caused a more chronic type of tuberculosis with most bacterial strains. At the same time, it made it possible to observe finer distinctions between the degree of pathogenicity of various strains, provided equal suspensions of cultures of the same age were compared under standardized conditions.

[2] Tween 80 is the proprietary name for the polyoxyethylene derivatives of Sorbitan monooleate, obtainable from the Atlas Powder Co., Wilmington, Delaware.

[3] Carworth Farms, New City, New York.

RESULTS

The results are summarized in tables 1 and 2. As may be seen in the tables, several facts were prominent and are listed as follows:

The susceptibility of these 20 bacterial strains to isoniazid varied over a wide range.

All of the strains were pathogenic for mice. Gross tuberculous lesions were found in the animals which died spontaneously as well as in the mice which were sacrificed after fifty-four days.

There was no correlation between the degree of virulence for mice and the degree of drug resistance. Of the four most virulent cultures, one was sensitive to 0.5 γ of isoniazid, one to 5.0 γ, whereas one grew in the presence of 50.0 γ of isoniazid per ml. of the two least pathogenic strains, one was inhibited by 0.5 γ of the drug and one lacked susceptibility to 50.0 γ of isoniazid per ml.

There was no correlation between the degree of virulence or the acquisition of drug resistance of the cultures of *M. tuberculosis* tested and the course of the tuberculosis in the corresponding patients during isoniazid therapy.

A considerable proportion of patients in this study became sputum "negative" during treatment. This is the reason why, in only a few cases, it was possible to compare drug susceptibility and pathogenicity of the tubercle bacilli isolated from the same patient at the beginning and the end of the study period (table 2).

DISCUSSION

It can be assumed that the acquisition of drug resistance as well as permanent changes in the virulence of a bacterial strain are based on a selection of mutants which are distinguished from the wild type by these very characteristics. Under certain conditions, these mutants develop more rapidly and abundantly than the wild type of organism and thus change the character of the strain. Furthermore, it can be assumed that virulence and drug susceptibility are transmitted by different genes which, a priori, would make it improbable that changes in the two qualities should be automatically associated. These assumptions do not preclude the occurrence of such association, but it has to be regarded as a fortuitous combination of two unrelated characteristics rather than as a representation of a causal connection. Indeed, in one instance in the present laboratory, it has been noted that a substrain of H37Rv, rendered isoniazid-resistant *in vitro*, lost its virulence to a very considerable extent (4). The experiments reported in the present paper, however, show that the combination of bacterial drug resistance acquired during clinical treatment and reduced pathogenicity of these bacteria for mice is an exception and not the rule, unless the mechanism of acquiring drug-fastness *in vitro* would be basically different from the process which occurs *in vivo*. Furthermore, the possibility remains that a bacterial suspension consists of a mixed population of organisms showing various degrees of drug resistance and pathogenicity (1).

It has been demonstrated many times that there is no parallel between the pathogenicity of a strain of *M. tuberculosis* for experimental animals and the

severity of the clinical condition of a patient from whom the organisms were isolated. This observation is again confirmed by the present tests. From a public health point of view, it seems obvious that a patient treated with isoniazid has to be regarded as a potential source of infection so long as he is discharging tubercle bacilli in the sputum regardless of whether his bacteria have become drug resistant and whether he has clinically improved during treatment.

The fact that the present experiments were done on a relatively small number of animals and bacterial strains and, moreover, that virulence tests were performed only in mice does not permit conclusions concerning the frequency at which changes in pathogenicity and in drug susceptibility do or do not occur simultaneously. The tests merely demonstrate that freshly isolated strains of tubercle bacilli which show a high degree of isoniazid resistance are not, *ipso facto*, nonpathogenic for mice.

SUMMARY

Tubercle bacilli isolated from the sputum of 20 patients who were receiving isoniazid treatment were tested for their drug susceptibility *in vitro* and for their pathogenicity for mice upon intravenous infection. Among 20 bacterial strains studied, there was no correlation between drug susceptibility and pathogenicity for mice, on the one hand, and between these two properties and the severity of the disease in the patient from whom the bacteria were isolated, on the other hand.

SUMARIO

La Sensibilidad a la Isoniacida y la Patogenicidad de los Bacilos Tuberculosos

Los bacilos tuberculosos aislados del esputo de 20 tuberculosos que estaban en vías de tratamiento con isoniacida fueron comprobados en cuanto a su fármacosensibilidad *in vitro* y su patogenicidad para los ratones infectados intravenosamente con ellos. Entre las 20 cepas bacterianas estudiadas, no hubo, por un lado, correlación entre la sensibilidad a la droga y la patogenicidad para los ratones, y por otro lado, tampoco entre dichas dos propiedades y la gravedad de la dolencia en los enfermos de quienes se habían aislado las bacterias.

RESUME

Sensibilité à l'isoniazide et pouvoir pathogène du bacille tuberculeux

Des bacilles tuberculeux, isolés de crachats provenant de 20 malades traités par l'isoniazide, ont été soumis à des tests de sensibilité à ce produit, *in vitro*, et leur pouvoir pathogène a été étudié chez la souris infectée par voie intraveineuse. Parmi les 20 souches étudiées, il n'y avait aucune corrélation entre leur sensibilité à l'isoniazide et leur pouvoir pathogène chez la souris, pas plus qu'entre ces deux propriétés et la gravité de l'affection chez les malades porteurs des bacilles isolés.

REFERENCES

(1) MIDDLEBROOK, G., AND COHN, M. L.: Some observations on the pathogenicity of isoniazid-resistant variants of tubercle bacilli; presented before the Colorado Trudeau Society, April 18, 1953 (submitted for publication to *Science*).

(2) PEIZER, L. R., AND SCHECHTER, C.: A new medium for bacteriologic diagnosis of tuberculosis, Am. J. Clin. Path., 1950, *20*, 682.

(3) DUBOS, R. J., AND MIDDLEBROOK, G.: Media for tubercle bacilli, Am. Rev. Tuberc., 1947, *56*, 334.

(4) BLOCH, H.: Unpublished observation.

OBSERVATIONS ON THE SEROLOGY OF PULMONARY TUBERCULOSIS[1]

A. RICHARDSON JONES[2] AND K. F. W. HINSON

(Received for publication February 20, 1953)

INTRODUCTION

The present writers have described elsewhere an antiglobulin modification of the Middlebrook-Dubos reaction (1). The modified reaction appears to offer some advantages with respect to its sensitivity, specificity, and usefulness as a weapon for the investigation of immune reactions associated with tuberculosis. The growing volume of literature on the subject has been reviewed in the previous report. It is relevant to the present communication, however, to note that Middlebrook (2), in describing the hemolytic modification of his test, observed that the distribution of positive reactions was not identical with respect to hemagglutinin and hemolysin.

The principle on which the Middlebrook-Dubos reaction is based is the conversion of a precipitin reaction into a hemagglutination reaction by the expedient of fixing the antigen onto the surface of an erythrocyte. In this case, tuberculin is fixed to the cell by what appears to be physical adsorption and the antibody with which this antigen reacts is probably an antituberculin found in the serum of patients with active tuberculosis. The present writers have carried the process a stage further by performing the Coombs' antiglobulin reaction on human erythrocytes which had first been treated wth tuberculin and then exposed to the action of tuberculous serum. The exact technique is presented below.

MATERIALS AND METHODS

Technique

Fresh human Group O Rh-negative erythrocytes were washed three times in isotonic saline and incubated for one hour with ten volumes of a 1:10 dilution of Lederle 4× Old Tuberculin. They were then washed again at least three times to remove all free or loosely adsorbed tuberculin, and the suspension made up to approximately 2 per cent. Equal volumes of this suspension and a 1:2 saline dilution of tuberculous serum were incubated for one hour, at the end of which time the cells were again washed three times and, finally, one drop of a diluted rabbit antihuman globulin serum was added to them. Observation of agglutination was carried out on glass slides at room temperature. Control sera of known positive and negative reaction were included in each batch of tests.

In addition, a conventional Middlebrook-Dubos hemagglutination titration was carried out on all sera.

Material Studied

Serum for examination was derived from three sources:

(*1*) From patients with active pulmonary tuberculosis (130 patients).

---

[1] From the Departments of Pathology and Clinical Pathology, The London Chest Hospital, London, England.

[2] Present address: Department of Pediatrics, Harvard University Medical School.

(2) From patients with nontuberculous intrathoracic disease who were admitted to the London Chest Hospital. In this group, tuberculosis was excluded by clinical, radiologic, and sputum examination. Frequently, pneumonectomy and lobectomy specimens from these patients allowed histologic examination to be made (44 patients).
(3) From healthy blood donors on the panel of the North London Blood Supply Depot (20 samples).

OBSERVATIONS

Serologic Results

When performing the antiglobulin reaction on cells which had previously shown a strong agglutination, it was noticed that, in the majority of cases (98 of 130 tuberculous sera), agglutinability was completely lost during the first wash. The cells became dispersed and were not susceptible to reagglutination when resuspended in inert serum. Ten sera behaved in the more usual way,

TABLE 1

DISTRIBUTION OF PATIENTS WITH RESPECT TO THEIR SEROLOGIC REACTIONS

AGGLUTININ REACTION AT 1:2	ANTIGLOBULIN REACTION AT 1:2	NUMBER OF PATIENTS
+	−	15
+	+	83
−	+	13
−	−	9
++	?	10

It is important to note that a limiting dilution of 1:2 has been taken as a criterion of positivity of the agglutinin when compiling this table. For assessing the clinical significance of the agglutinin, however, the example of other workers has been followed and a titer of 1:8 has been used.

however, in so far as the cells with which they had been treated retained their agglutinability after repeated washing. It was also noticed that the presence of hemagglutination did not necessarily mean that the subsequent antiglobulin test would be positive, nor did the absence of hemagglutination imply a negative antiglobulin reaction. The distribution of these reactions in the tuberculous sera which were examined is shown in table 1.

The provisional interpretation of these results was that antibodies of two main physical types existed but that the strongly reacting agglutinin which resisted washing was probably a variant of the more easily removed agglutinin. These antibodies have been designated *Type I* and *Type II* and have been defined as follows:

Type I. An agglutinin which reacts weakly with antigen and is easily dissociated from it. No obvious relationship exists between dissociability and titer.
Type II. A nonagglutinin which reacts strongly with antigen and is dissociated from it with difficulty. Its presence is revealed by the antiglobulin reaction but not by titration in bovine albumin.

Further experiments were carried out in an endeavor to test the validity of these assumptions.

Repeated treatment of tuberculin-sensitized erythrocytes with a serum which was thought to contain only *Type I* antibody (agglutinin titer, 1:64; antiglobulin reaction, negative) failed to convert the negative antiglobulin reaction into a positive one. Cells treated in this way were then suspended in a *Type II* serum (agglutinin titer, zero; antiglobulin reaction, positive). After incubation with this serum for one hour, the antiglobulin reaction of the cells was found to be strongly positive, but the agglutinin reaction had diminished in strength.

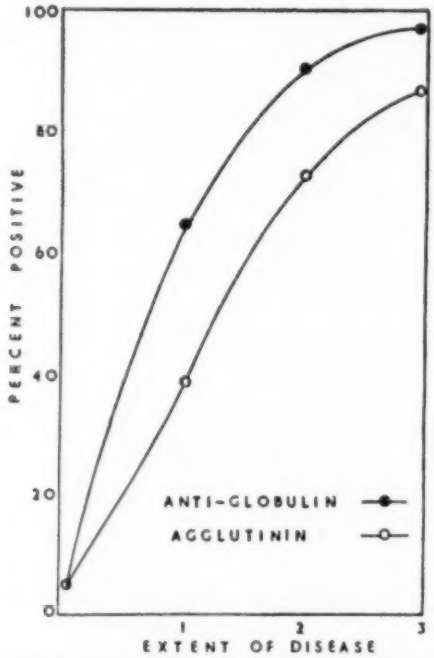


FIG. 1. The correlation between the anatomic extent of the pulmonary lesion and the immune response. The zero value on the abscissa represents nontuberculous subjects.

As a corollary to the previous experiment, tuberculin-sensitized cells were treated with *Type II* serum, with no evidence of agglutination appearing after three such treatments. However, replacement of this serum by one containing *Type I* antibody resulted in agglutination of the cells up to the expected limiting dilution, the antiglobulin reaction of the 1:2 tube being unchanged.

It appears from these results that such sera are not capable of exerting a mutual blocking effect. The failure of *Type II* to block the haptenic determinants for *Type I* is strongly in favor of the antibodies being of differing specificity. However, when the reverse situation is considered, the lability of the *Type*

I antigen-antibody bond raises the possibility of *Type I* dissociating in favor of *Type II* when competition exists between the two. The reduction of the observed strength of agglutination (by the agglutinin component) in the first experiment favors this view.

Clinical Results

It has already been shown by the present writers (1) that there is a striking relationship between the anatomic extent of pulmonary tuberculosis and the

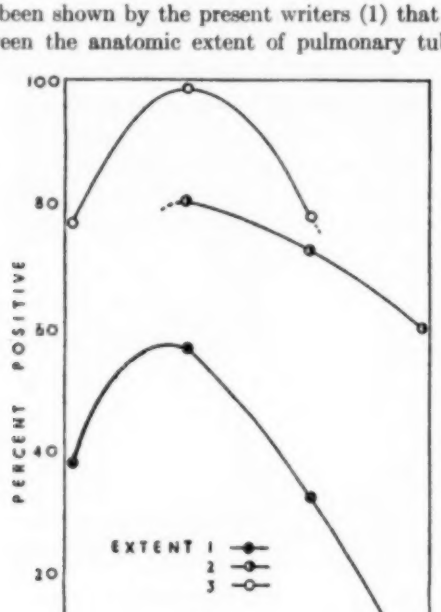


FIG. 2. Independence of age and extent of disease in their effect on the hemagglutination reaction. Definition of age groups is as follows: (*1*) less than 20 years; (*2*) 20 to 30 years; (*3*) 30 to 40 years; (*4*) more than 40 years.

incidence of positive hemagglutination reactions. The relationship still obtains when the incidence of positive antiglobulin reactions is plotted against the extent of the disease, but it is evident from inspection of figure 1 that the test described in the present report is significantly more sensitive than the conventional hemagglutination test. In spite of the greater sensitivity, the incidence of positive results in the nontuberculous control sera is no higher; this would seem to imply a higher degree of specificity.

In most other respects, the antiglobulin modification parallels the results of the conventional test while showing an increased sensitivity ranging from 10

to 15 per cent. One exception is the distribution of response with respect to age groups. In figure 2 may be seen the way in which age influences the immune response of the individual to different extents of tuberculosis when only the hemagglutination reaction is considered.

In figure 3 may be seen the variation of response as measured by the antiglobulin modification. The independence of age and extent is not now as obvious as in figure 2, which would seem to indicate the greater value of this modification as an aid to diagnosis.

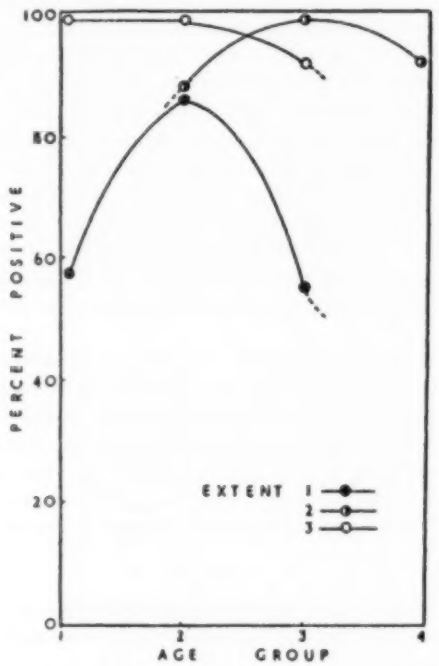


FIG. 3. The reduced independence of patient's age and extent of disease when the antiglobulin reaction is considered. The age group definition is the same as in figure 2.

DISCUSSION

As mentioned previously, Middlebrook suspected that more than one antibody might be involved in the reaction between tuberculin-sensitized erythrocytes and tuberculous serum. That the present findings support this supposition is hardly surprising in view of the known complexity of the chemical structure of tuberculin (3).

It was observed by Middlebrook and Dubos (4) and confirmed by Hilson and Elek (5) that the most important antigenic substances from the point of view of this reaction are polysaccharides. The observation that purified protein deriva-

tive (PPD) is also capable of acting as antigen has been confirmed by one of the present writers (A.R.J.). This in no way mitigates the antigenic role of polysaccharide, as Seibert (3) has shown that complete separation of these compounds from the protein of tuberculin is fraught with difficulty, and it is probable that most PPD preparations contain up to 2 per cent of polysaccharide.

There can be little doubt that the Middlebrook-Dubos reaction and the several modifications of it propounded from time to time detect antibodies to the products of metabolism of the tubercle bacillus and almost certainly do not detect antibodies to the somatic antigens of the organism. The increasing incidence of positive reactions with increasing extent of disease would seem to be evidence against the antibodies representing a protective mechanism. The interpretation of the present writers is that the immune response is approximately proportional to the number of viable tubercle bacilli existing in the host. When the rate of multiplication of the organism (and, hence, the rate of production of antigenic metabolic products) is reduced by the administration of streptomycin, the incidence of positive reactions is found to fall (6). In the present series, 63 per cent of tuberculous patients who did not receive streptomycin possessed hemagglutinins, while these could be demonstrated in only 48 per cent of patients who received the drug. Application of the chi-square test for significance showed this to be a borderline result, but it may, nevertheless, be regarded as being strongly suggestive.

Neither the hemagglutinin reaction nor the antiglobulin modification described here satisfies the most important criterion of a laboratory test for the diagnosis of tuberculosis, which is that unequivocal results should be obtained with clinically debatable lesions. However, the increased sensitivity of the present test, together with its relative freedom from the influence of the patient's age, would seem to recommend its usefulness as an adjuvant to the diagnosis of moderate and extensive pulmonary infiltrations of unknown etiology.

SUMMARY

A modification of the antituberculin hemagglutination reaction is described. Evidence is adduced for the possible existence of two antituberculins of probably differing specificity.

SUMARIO

Algunas Observaciones Relativas a la Serología de la Tuberculosis Pulmonar

Descríbese una modificación de la reacción de hemaglutinación con antituberculina. Apórtanse datos acerca de la posible existencia de dos antituberculinas dotadas probablemente de distinta especificidad.

RESUME

Quelques observations sur la sérologie dans la tuberculose pulmonaire

Une modification de la réaction d'hémagglutination antituberculinique est décrite. Les résultats obtenus permettent d'envisager l'existence de deux antituberculines de spécificités différentes.

Acknowledgments

Acknowledgments are due to the Consultant Staff of the London Chest Hospital for permission to examine the serum of their patients, and to the Director of the North London Blood Supply Depot for the supply of normal serum samples. The tuberculin used was donated by Messrs. Cyanamid Products Limited.

REFERENCES

(1) Hinson, K. F. W., Richardson Jones, A., and Chamberlin, J. A. The Middlebrook-Dubos reaction in relation to the clinical aspects of pulmonary tuberculosis, Brit. J. Tuberc., 1952, *46*, 50.

(2) Middlebrook, G.: A hemolytic modification of the hemagglutination test for antibodies against tubercle bacillus antigens, J. Clin. Investigation, 1950, *29*, 1480.

(3) Seibert, F. B., and Dufour, E.: A study of certain problems in the use of standard tuberculin: Fractionation of PPD, standardization of tuberculins, and the question of sensitization, Am. Rev. Tuberc., 1948, *58*, 363.

(4) Middlebrook, G., and Dubos, R. J.: Specific serum agglutination of erythrocytes sensitized with extracts of tubercle bacilli, J. Exper. Med., 1948, *88*, 521.

(5) Hilson, G. R. F., and Elek, S. D.: The haemagglutination reaction in tuberculosis, J. Clin. Path., 1951, *4*, 158.

(6) Gernez-Rieux, C., and Tacquet, A.: La réaction d'hemagglutination dans la tuberculose, Ann. Inst. Pasteur de Lille, 1950, *3*, 1.

STUDIES OF CELLULAR LYSIS IN TUBERCULIN SENSITIVITY[1,2]

BYRON H. WAKSMAN

With the technical assistance of Margaret P. Carroll and Donald Gaulitz

(Received for publication April 29, 1953)

INTRODUCTION

The damage of cells cultured from tuberculous animals by tuberculin *in vitro* has formed the basis of some theories of the mechanism of tuberculin sensitivity. The existence of this tissue culture inhibition (TCI) is attested by a number of careful observations (1, 2, 3, 4, 5); yet studies in other laboratories have failed to demonstrate it (6), have attributed it to a generally decreased vitality of tuberculous tissue (7), or have actually found stimulation rather than inhibition as the predominant effect in such cultures (8, 9, 10). More recently, lysis of circulating leukocytes by tuberculin ("lympholysis") has been demonstrated and has been considered to be another manifestation of the same inhibitory process (11, 12, 13, 14). While no information has been obtained to explain the detailed mechanism of tissue culture inhibition, "lympholysis" has been found to be associated with the presence of a plasma factor, apparently released by circulating lymphocytes (15, 16), and to require the presence of complement (17). The following experiments were carried out in an attempt to determine the relation of the "lympholysis" phenomenon to the tissue culture phenomenon and in the hope of finding a basis for some of the discrepant findings in tissue culture.

MATERIALS AND METHODS

Tissue culture: Tissues were removed promptly from experimental animals, cut into 1 to 2 mm. fragments within an hour, and rinsed two or more times. Within three hours, 4 to 6 explants were planted in a thin clot of heparinized 33 per cent plasma along one side of 16 x 150 mm. tubes. One milliliter of freshly prepared nutrient, containing 40 per cent horse serum (Cappel Laboratories) and 7.5 per cent ten-day-old chick embryo extract, covered the explants. The tubes were tightly stoppered, room air constituting the gas phase, and were kept almost horizontal in wire racks. The medium was not changed in these short-term experiments. In certain instances, one-fourth to three-fourths of the horse serum was replaced by pooled guinea pig serum as a source of complement. The complement remained stable for many months at −20°C., as did the embryo extract. Old Tuberculin (OT), obtained from the Massachusetts State Laboratories, was also used in final dilutions between 1:50 and 1:150. Repeated tests with the conventional hemolytic system showed no complement activity in any of the constituents or in any complete nutrients except those containing added complement. Tests of each variable were set up in duplicate tubes except in experiment 5 (4 guinea pigs).

Cultures were observed microscopically for four or five days, and daily estimates were made of the number and quality of cells (in particular, macrophages and fibroblasts) around each explant. The pH was recorded daily and provided an additional criterion of the meta-

[1] From the Departments of Neuropathology of the Harvard Medical School and the Massachusetts General Hospital.

[2] This study was aided by a grant from the National Multiple Sclerosis Society.

bolic activity of the cultures. For graphic comparison of the responses of cultures grown under different conditions, a "colony index" was calculated as follows. When the number of cells visible around an explant was between 1 and 5, it was recorded as 0.5; when it was approximately 10, as 1.0; 25, 2.0; 50, 3.0; very profuse, 4.0. These values were averaged for all of the explants in all of the tubes containing a particular nutrient. In the case of macrophages, this average was multiplied by the estimated percentage of cells living and by the average distance of migration as a proportion of the maximum distance of migration in control tubes.

"Lympholysis" counts: The technique of Favour and his associates (12) was followed in most details. Fresh blood was obtained from each test animal with the use of only enough heparin (Liquaemin, Organon, containing 10 mg. of heparin sodium per ml. and 0.45 per cent phenol) to moisten the syringe. Four-tenths of a milliliter was mixed in a siliconed tube

TABLE 1

PROTOCOL OF READINGS ON GUINEA PIG NO. 2, EXPERIMENT 9, SPLEEN CULTURE
THIRD DAY

MEDIUM		TUBE NUMBER	MACROPHAGES				FIBROBLASTS	
			Average Number of Cells Per Colony	Per Cent Alive	Migration in Explant Diameters	Calculated Colony Index*	Number of Cells Per Colony†	Colony Index*
Saline	20 per cent complement	1	>100	90	5.0	3.6	0, 0, 50, 25, 10	1.5
		2	>100	90‡	5.0		25, 25, 25, 50, 0	
	No complement	1	50	90‡	4.0	2.4	50, 5, 0, 0	1.3
		2	50	70	1.0 2.0		10, 50, 50, 5, 10	
OT 1:144	20 per cent complement	1	25	30	1.0 2.0	0.5	5, 0, 5, 0, 0, 5	0.9
		2	25	30	1.0		0, 25, 10, 50, 50, 0	
	No complement	1	5	0	0.5	0.5	0, 5, 50, 5	0.7
		2	0	—	—		5, 5, 5, 0	

* See *Methods* for method of calculation.
† Explants recorded in order from end of tube.
‡ Cells granular but living.

with 0.1 ml. of antigen (OT 1:5 or 1:10) or saline. Preliminary dialysis of antigen was unnecessary, since the dilutions used did not cause lysis of the leukocytes of normal blood. The tubes were tightly stoppered and incubated at 37°C. for one hour in a slanting holder rotating approximately once a minute. Counts of all the squares of the standard hemocytometer chamber were made at the beginning and end of an hour, with the same dilution pipette for each tube. When each manipulation was carried out with great care, replicate counts could be obtained which varied by less than 3 or 4 per cent. As, however, discrepancies caused by abnormal distributions of cells in the hemocytometer chamber occurred not infrequently, changes of less than 10 per cent were not considered significant. In bloods showing a high erythrocyte sedimentation rate, clumping of cells made consistent counts unattainable. Control counts, obtained in the tubes to which only saline was added, sometimes decreased 10 or 15 per cent.

Animals, inoculations, and skin testing: As one of the objectives of these experiments was to reveal possible differences in the pattern of response of mature, healthy rabbits and guinea pigs to tubercle bacilli, the animals used were diverse in weight, sex, and origin,

FIG. 1. Experiment 6, guinea pig No. 8. Living spleen cultures photographed on third day (×200). *A*. Healthy macrophages at edge of zone of migration, in culture grown in medium containing 20 per cent complement. *B*. Area near explant, in medium containing OT, 1:144, and 20 per cent complement. Note absence of living cells. *C*. Small explant showing proliferation of fibroblasts, in medium containing OT, 1:144.

although alike in any one experiment. The methods of inoculation are detailed in the tables. Certain groups of animals were inoculated with various amounts of heat-killed, human-type tubercle bacilli incorporated in Bayol F, a bland mineral oil; others received sputum which contained tubercle bacilli; and still others a living eight-week-old culture of recently iso-

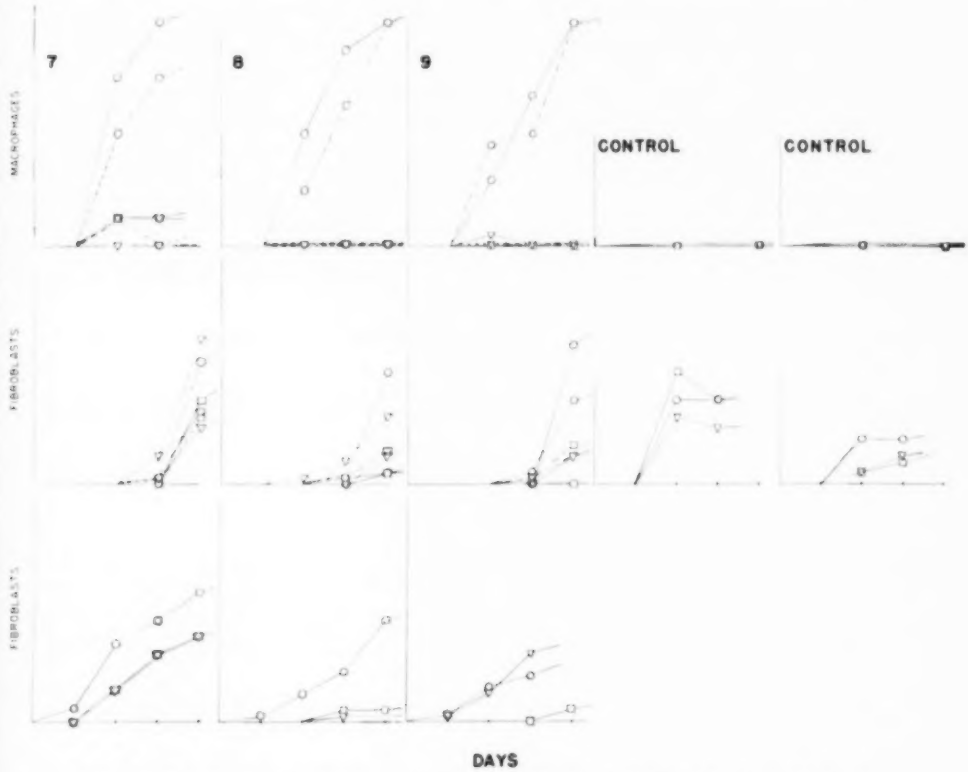


FIG. 2. Graphs of colony index in spleen and lymph node cultures of 3 tuberculin-sensitive guinea pigs and 2 normal controls of experiment 6. Medium contains: ○– – –, neither OT nor complement; ○——, 20 per cent complement; ▽– – –, OT, 1:144; ▽——, OT, 1:144 and 20 per cent complement; □– – –, OT, 1:70; □——, OT, 1:70 and 20 per cent complement.

lated, virulent organisms. Skin testing was ordinarily performed in the usual manner with OT. In a number of instances, however, a suspension of homologous heat-killed organisms in saline was employed (18).

RESULTS

To illustrate the method of evaluating tissue culture response, a typical protocol and the calculated colony indices are shown in table 1. It may be seen that the addition of guinea pig serum (complement) stimulated cell colonies, whether

in the presence or absence of OT. It had no apparent influence on the inhibition of these colonies by OT. The inhibiting effect was definite in macrophages and less evident in fibroblasts. Figure 1 is taken from a spleen culture of another animal and illustrates a typical response, macrophages being entirely inhibited by the presence of tuberculin where fibroblasts are relatively unaffected.

The type of variation in the response to tuberculin of spleen and lymph node cultures is illustrated by the experiments shown in figures 2 and 3. As few macrophages migrated from the lymph node explants, a graph of these is not shown. Colony indices, calculated in the same manner as those shown in table 1, were used as ordinates in these graphs; they are not assumed to represent any absolute

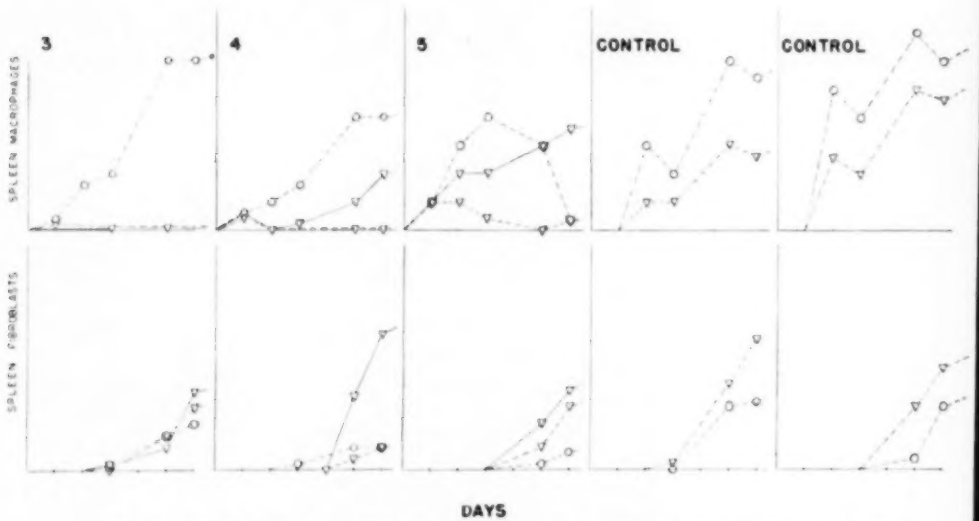


FIG. 3. Graphs of colony index in spleen cultures of 3 tuberculin-sensitive guinea pigs and 2 normal controls of experiment 9. Medium contains: ○——, neither OT nor complement; ▽- - - -, OT, 1:140 but no complement; and ▽——, OT, 1:140 and 20 per cent complement.

value but to have relative significance only. The first point of interest is the fact that, in experiment 6, the control tissues seemed less vigorous than tissues from the sensitized guinea pigs. In fact, no macrophages migrated from the normal spleens cultured under the conditions of this experiment. A similar difference between the activity of normal and sensitive tissues was observed frequently in the experiments (*vide infra*, tables 4 and 5). The second point illustrated is that fibroblasts were affected by tuberculin to quite different degrees in different instances where macrophages were almost entirely inhibited. Indeed, in Nos. 4 and 5 of experiment 9, fibroblasts appeared to be stimulated, particularly under the better growth conditions resulting from the addition of homologous serum (complement) to the medium. In these two cases, the added complement also

seemed to reverse in part the inhibition of macrophages. In general, the lymph node cultures behaved similarly to the spleen cultures.

An experiment was performed with heated medium and no plasma (table 2) in order to meet the possibility that residual complementary activity might be present in the constituents of the medium used in other experiments of this series. Explants were washed five times before planting. Cultures were set up in small glass chambers, permitting high-power observation. The complete nutrient was heated twenty minutes at 56°C. before use. The tuberculin inhibition of macrophage colonies was quite recognizable under these conditions. In this experiment, the superior growth of the tissue from the sensitized animal may again be seen. The cells of the control did not migrate well in the presence of tuberculin but remained healthy in appearance.

In table 3 are presented the results of repeated skin tests and "lympholysis" tests in the animals of experiment 6, together with the post-mortem and tissue culture findings. It is clear that "lympholysis" occurred, if at all, only early in the course of sensitization. It was conspicuously absent at a time when skin sensitivity was marked and inhibition of macrophages in tissue culture was strikingly demonstrable. It is also noteworthy that tissue culture inhibition was evident in animals which did not show grossly necrotic skin responses to 10 mg. of OT.

Summarized data of the guinea pig and rabbit experiments carried out are presented in tables 4 and 5. The migration of cells from the tuberculous tissue exceeded that of cells from the normal control in 10 of the 13 rabbits and 10 of the 13 guinea pigs cultured. Added complement did not enhance tissue culture inhibition in any of the 7 rabbit or 10 guinea pig experiments in which it was tried; in 2 instances, it seemed rather to interfere with the effect. Of the 23 animals showing grossly nonnecrotic skin reactions shortly before the time of death, 10 showed tissue culture inhibition of macrophages, fibroblasts, or both; of these, 2 showed "lympholysis", 5 did not, and 3 were not tested. Seven showed no tissue culture inhibition; of these, 2 showed "lympholysis", one did not, and 4 were not tested. Of 6 not cultured post mortem, 4 showed "lympholysis" and 2 did not. Of the 13 animals showing necrotic skin reactions, 9 showed a definite inhibition in tissue culture; of these, 2 showed "lympholysis", 5 did not, and 2 were not tested. Four were not cultured post mortem; these did not show "lympholysis."

In short, a positive tissue culture inhibition was observed in every animal tested of those with the highest degree of skin reactivity and in approximately one-half of those with lesser reactivity. "Lympholysis," on the other hand, was distributed between the groups at random and was, if anything, less frequent in the more skin-sensitive groups. The findings were comparable in rabbits and guinea pigs.

DISCUSSION

It appears from the data presented that "lympholysis" is not correlated in any way with tissue culture inhibition. This conclusion accords well with other

available information regarding each of these *in vitro* phenomena. Different cells are involved. Macrophages, fibroblasts, and liver cells have been shown to be inhibited in tissue culture by tuberculin (1, 2, 3, 4, 5), while lymphocytes (14) or lymphocytes and polymorphonuclear leukocytes (19, 20) are affected in "lympholysis". It is impossible at present to interpret short-term tissue culture experiments involving granulocytes (4, 21). Complement appears not to be necessary for tissue culture inhibition but to be essential for "lympholysis" (17). Tissue culture inhibition depends on the state of the cells themselves and not on any serum or plasma factor (1, 2, 3, 4, and these experiments), whereas "lympholysis" depends essentially on a circulating antibody and can be produced in normal cells (15, 20). This antibody seems entirely comparable to erythrocyte lysing antibodies well known in tuberculosis (22) and to leukocyte lysing antibodies seen in simple protein sensitization (23) or atopic allergy (24).

TABLE 2

PROTOCOL OF READINGS ON THIRD DAY, SPLEEN CULTURE, HEATED MEDIUM AND NO PLASMA*

MEDIUM	CHAMBER NUMBER	TUBERCULOUS GUINEA PIG†				NORMAL GUINEA PIG			
		Number of Explants	Average Number of Cells Per Colony‡	Per Cent Alive	Migration in Explant Diameters	Number of Explants	Average Number of Cells Per Colony‡	Per Cent Alive	Migration in Explant Diameters
Saline	1	2	50	100	1.0, 1.25	3	10(1/3)	100	0.5
	2	3	40	100	0.5–1.5	3	20	100	0.5–1.0
	3	3	50	100	0.75–1.75	2	15	100	0.5, 1.0
	4	—	—	—	—	2	40	100	0.5, 1.0
	5	—	—	—	—	2	25(1/2)	100	0.8
OT 1:125	1	3	0	—	—	2	10	100	0.2
	2	3	0	—	—	3	5	100	0.1
	3	4	5(1/4)	100	0.25	2	10	100	0.2
	4	4	5(1/4)	20	0.5	2	5	100	0.3
	5	—	—	—	—	3	5(1/3)	100	0.3

* Complete nutrient heated at 56°C. for 20 minutes immediately before use. Macrophages only are shown, as fibroblasts appeared on fourth day and grew poorly on glass.

† Guinea pig inoculated 25 days earlier with 1.0 ml. of killed tubercle bacilli in Bayol F, 4 mg. per ml., given subcutaneously.

‡ Proportion of explants showing cell migration given in parentheses, if less than all.

The fact that tissue culture inhibition is independent of circulating antibody and of complement makes this phenomenon quite different from other known immunologic types of cell damage. That tuberculin under appropriate conditions appeared to stimulate cell colonies rather than to inhibit them or to stimulate one cell type while inhibiting another is perhaps an example of the threshold effects seen with many types of inhibitors. While the precise factors determining these variations in response remain to be investigated, it is evident that they are dependent on the conditions of culture. The evidence presented suggests further

that inhibition in tissue cultures as employed is correlated with the necrotic type of skin reaction rather than with the milder degrees of skin reactivity. A priori, such a possibility seems reasonable since it is unlikely that the skin

TABLE 3

COMPARISON OF "LYMPHOLYSIS" WITH TISSUE CULTURE INHIBITION AND WITH SKIN SENSITIVITY TO TUBERCULIN

Experiment 6

DAY	GUINEA PIG NO. 7*		GUINEA PIG NO. 8*		GUINEA PIG NO. 9*	
	Skin Reaction†	Leukocyte Lysis‡	Skin Reaction	Leukocyte Lysis	Skin Reaction	Leukocyte Lysis
11	—	+5.1 +0.3	—	**+6.6** **9.9**	—	+10.0 +22.0§
15	0	—	5 mm. of induration	—	5 mm. of induration	—
20	—	**4.9** **14.8**	—	6.3 +7.7	—	2.3 +20.0§
22	—	+0.1 +5.1	—	**0.9** **6.5**	—	5.3 3.4
23	10 mm. of induration and erythema	—	7 mm. of induration	—	10 mm. of induration	—
27	—	3.4 0.2	—	4.6 0.8	—	+3.2 +0.4
30	12 mm. of induration and erythema; 5 mm. of necrosis	—	10 mm. of induration and erythema	—	10 mm. of induration and erythema	—
34	—	+1.4 +7.2	—	— +4.7	—	11.6 11.3
Findings at post mortem, thirty seventh day	Massive local lymphatic involvement with extension. Few tubercles in spleen		Moderate involvement of local nodes		Massive involvement of local and retroperitoneal nodes. Many tubercles in spleen	
Tissue culture inhibition:						
Spleen macrophages	+++		++++		++++	
fibroblasts	0		+		++	
Node macrophages,	+++		—		—	
fibroblasts	±		+++		+	

* Inoculated subcutaneously with 1.0 ml. of a heavy saline suspension of an eight week old culture of virulent human tubercle bacilli.

† Skin tested with OT 1:10, readings at 48 hours.

‡ Upper figure represents per cent of fall in total count in saline tube; lower figure, the per cent fall in tube to which OT 1:10 has been added.

§ Severe clumping in these tubes.

reaction, which is primarily proliferative and infiltrative, depends upon what is essentially a cell-destroying mechanism. Most earlier studies of tissue culture inhibition were carried out with tissues from animals showing necrotic skin responses.

The results of the present experiments offer no support for the contention that

TABLE 4

Correlative Summary of Experimental Data in All Rabbits of Present Study

Rabbit	Inoculation*	Skin test			"Lympholysis"		Tissue culture					
		Day	Agent	Reaction†	Day	Decrement‡	Day	Tissue	Inhibition of: Fibroblasts	Inhibition of: Macrophages	Effect of Complement	Colony Size Relative to Control§
				mm.		*per cent*						
A-2	4 mg. per ml. in oil, id x4, repeated at 7 days	13	OT, undiluted	20 (8)	—	—	38	Node	+	+	—	>
1-646	2 mg. per ml. in oil, id x4	10	Tubercle bacilli, 0.2 mg. per ml. saline	10	14	−5.5	15	Node	±	0	—	>
1-647	2 mg. per ml. in oil, id x4	10	Tubercle bacilli, 0.2 mg. per ml. in saline	10	—	—	13	Node	0	++++	—	>
1-649	2 mg. per ml. in oil, id x4	10	Tubercle bacilli, 0.2 mg. per ml. in saline	15	—	—	13	Node	±	±	—	>
3-600	2 mg. per ml. in oil, id x1	10	Tubercle bacilli, 0.2 mg. per ml. in saline	17	—	—	28	Node	0	0	0	>
3-616	2 mg. per ml. in oil, id x1	48	Tubercle bacilli, 0.2 mg. per ml. in saline	5	52	−11.4	—	—	—	—	—	—
3-619	2 mg. per ml. in oil, id x1	48	Tubercle bacilli, 0.2 mg. per ml. in saline	7	52	−13.3	—	—	—	—	—	—
3-635	2 mg. per ml. in oil, id x1	10	Tubercle bacilli, 0.2 mg. per ml. in saline	15	11	−6.6	13	Node	0	0	—	>
5C36	2 mg. per ml. in oil, id x1	10	Tubercle bacilli, 0.2 mg. per ml. in saline	15	—	—	12	Node	0	0	—	>
5J73	2 mg. per ml. in oil, id x1	10	Tubercle bacilli, 0.2 mg. per ml. in saline	15	—	—	13	Node	0	0	—	>
8J01	2 mg. per ml. in oil, id x1	10	Tubercle bacilli, 0.2 mg. per ml. in saline	15	—	—	28	Node	+	++	0	>

6-526	2 mg. per ml. in oil, id x4; virulent human tubercle bacilli, 1 ml. sc at 54 days	69	OT, 1:10	10	68	+3.6	—	—	—	—	—	—
		77	OT, 1:10	20	74	+0.6						
		84	OT, 1:10	8	88	+3.8						
6-527	2 mg. per ml. in oil, id x4; virulent human tubercle bacilli, 1 ml. sc at 54 days	69	OT, 1:10	5	14	−4.8	77	Node	0	0	0	<
					20	+11.9						
6-539	2 mg. per ml. in oil, id x4; virulent human tubercle bacilli, 1 ml. sc at 54 days	69	OT, 1:10	3	68	+10.8	—	—	—	—	—	—
		77	OT, 1:10	7	74	−4.9						
		84	OT, 1:10	8	88	−0.8						
6-832	Virulent human tubercle bacilli, 1 ml. sc	23	OT, 1:10	20	14	−5.8	49	Spleen	0	0	0	>
		30	OT, 1:10	8	20	−8.6						
					27	−1.7						
					34	+9.8						
9-652	4 mg. per ml. in oil, id x4	26	OT, 1:10	20 (6)	26	−32.9	33	Buffy coat	—	++	0	=
							69	Spleen	+	++	0	=
13-651	4 mg. per ml. in oil, id x4	26	OT, 1:10	30 (7)	26	+6.3	—	—	—	—	—	—
13-653	4 mg. per ml. in oil, id x4	26	OT, 1:10	15	26	−25.4	—	—	—	—	—	—
13-654	4 mg. per ml. in oil, id x4	26	OT, 1:10	20	26	−9.6	—	—	—	—	—	—
13-655	4 mg. per ml. in oil, id x4	26	OT, 1:10	30	26	−8.3	69	Spleen	0	++	0	=

* id, intradermal (0.1 ml. doses in footpads); sc, subcutaneous (anteromedial aspect of thighs).

† Average diameter of indurated area. Diameter of necrosis in parentheses.

‡ Decrement, difference between per cent of change in test tube and that in saline tube.

§ >, greater than control; <, less; =, equal.

‖ Lysis counts performed in duplicate.

TABLE 5

Correlative Summary of Experimental Data in All Guinea Pigs of Present Study

Guinea pig	Inoculation*	Skin test			"Lympholysis"		Tissue culture					
		Day	Agent	Reaction†	Day	Decrement‡	Day	Tissue	Inhibition of: Fibroblasts	Inhibition of: Macrophages	Effect of Complement	Colony Size Relative to Control§
				mm.		*per cent*						
5-4	2 mg. per ml. in oil, id x1	14	OT, 1:10	10	13	−20.9	19	Uninvolved node	0	±	0	>
					15	−9.5						
					19	+12.2						
5-5	2 mg. per ml. in oil, id x1	14	OT, 1:10	8	13	+16.8	19	Uninvolved node	0	0	—	>
					15	−33.0						
					19	−3.7						
5-825	Tuberculous sputum sc	24	OT 1:10	8	13	−9.8	30	Involved node	++	0	—	>
					19	+9.0						
5-838	Tuberculous sputum sc	24	OT, 1:10	15 (5)	13	−10.4	30	Involved node	+	±	—	>
					15	+1.8						
6-7 ‖	Virulent human tubercle bacilli, 1 ml. sc.	30	OT, 1:10	12 (5)	34	+5.8	37	Spleen	0	+++	0	>
								Node	±	+++		
6-8 ‖	Virulent human tubercle bacilli, 1 ml. sc	30	OT, 1:10	10	34	+4.7	37	Spleen	+	++++	0	>
								Node	+++	—		
6-9 ‖	Virulent human tubercle bacilli, 1 ml. sc	30	OT, 1:10	10	34	+0.3	37	Spleen	++	++++	0	>
								Node	+	—		
6-1	2 mg. per ml. in oil, id x1; 10 mg. in oil sc at 20 days	14	OT, 1:10	15	13	−1.7	—	—	—		—	—
		35	OT, 1:10	Shock	15	+5.9						
6-2	2 mg. per ml. in oil, id x1; 10 mg. in oil sc at 20 days	14	OT, 1:10	15	13	+19.3	—	—	—		—	—
		35	OT, 1:10	Shock	15	+3.7						
9-1	10 mg. per ml., 1 ml. sc	35	OT, 1:10	15 (8)	35	−0.8	42	Spleen	0	++++	0	>
					41	+14.1		Node	0	—		
9-2	10 mg. per ml., 1 ml. sc	35	OT, 1:10	20 (10)	35	+9.1	42	Spleen	+	++++	0	>
					41	−25.0		Node	0	0		
9-3	Virulent human tubercle bacilli, 0.5 ml. sc	21	OT, 1:100	10	21	+15.4	28	Spleen	0	++++	0	=
9-4	Virulent human tubercle bacilli, 0.5 ml. sc	21	OT, 1:100	10 (3)	21	−1.2	28	Spleen	0	+++	Inhibit OT effect	=
9-5	Virulent human tubercle bacilli, 0.5 ml. sc	21	OT, 1:100	10 (4)	21	+16.4	28	Spleen	0	++	Inhibit OT effect	=
9-6	Virulent human tubercle bacilli, 0.5 ml. sc	21	OT, 1:100	10 (5)	21	+5.0	—	—	—		—	—
18-2	4 mg. per ml. in oil, id x4	22	OT, 1:100	15 (10)	—	—	25	Spleen	0	+++	0	>

*, †, ‡, § See table 4.

‖ Fuller details are given in table 3.

cells of tuberculous animals have decreased vitality and, therefore, are susceptible in tissue culture to the general toxicity of tuberculin (7). On the contrary, in the great majority of the cultures, more migration of cells occurred from tuberculous tissues than from normal tissues. This finding accords well with the increased nonspecific activity of the reticulo-endothelial system demonstrated in tuberculosis (25).

No correlation is found between "lympholysis" and tuberculin skin sensitivity (*see also* (12)). There seems to be no basis, therefore, for relating "lympholysis" with the necrosis of the tuberculin skin reaction. It remains to be determined whether the fact that lymphocytes produce "lympholytic" antibody (16) and also are lysed in "lympholysis" (14, 19) is connected with the fact that they can transfer tuberculin skin reactivity passively (26, 27).

SUMMARY

The "lympholysis" phenomenon is correlated neither with the inhibition of macrophages and fibroblasts in tissue culture by tuberculin nor with the tuberculin skin reaction in sensitized guinea pigs or rabbits.

Tissue culture inhibition is correlated with skin reactivity and is found in all animals with necrotic skin reactions to 10 mg. of Old Tuberculin (OT).

Tissue culture inhibition can occur in the absence of complement.

Tissues taken from tuberculin-sensitized animals show greater activity *in vitro* in most instances than tissues of normal controls.

Fibroblasts are affected by tuberculin to a much less degree than macrophages and, in certain cases, appear to be stimulated rather than inhibited.

The character of the culture medium may affect the obtaining of the characteristic inhibition effect of tuberculin added to tissue cultures.

SUMARIO

Estudios de la Citólisis en la Sensibilidad a la Tuberculina

El fenómeno de la "linfólisis" no se correlaciona ni con la inhibición de los macrófagos y los fibroblastos en los cultivos de tejido por la tuberculina ni con la cutirreacción a la tuberculina en los cobayos o conejos sensibilizados.

La inhibición de los cultivos histológicos se correlaciona con la reactividad cutánea, observándose en todos los animales que muestran cutirreaciones necróticas a 10 mg. de tuberculina antigua (TA).

Puede presentarse inhibición de los cultivos de tejido sin haber complemento.

Los tejidos obtenidos de animales sensibilizados a la tuberculina revelan, en la mayor parte de los casos, mayor actividad *in vitro* que los tejidos de testigos normales.

Los fibroblastos son afectados por la tuberculina mucho menos que los macrófagos, y en ciertos casos parece que son estimulados más bien que inhibidos.

La naturaleza del medio de cultivo tal vez afecte la obtención del típico efecto inhibidor de la tuberculina agregada a los cultivos histológicos.

RESUME

Etudes sur la lyse cellulaire dans la sensibilité à la tuberculine

Le phénomène de la "lympholyse" est sans relation avec l'inhibition des macrophages et des fibroblastes, soit dans la culture des tissus avec la tuberculine (TCI), soit dans la réaction cutanée à la tuberculine des cobayes ou des lapins sensibilisés.

L'inhibition de la culture des tissus (TCI) est en corrélation avec la réaction cutanée, elle est observée chez tous les animaux; la dose de 10 mg. de tuberculine de Koch (OT) donne des réactions cutanées nécrotiques.

L'inhibition des cultures tissulaires (TCI) peut se produire en l'absence de complément. Dans la plupart des cas, les tissus prélevés chez les animaux sensibilisés à la tuberculine montrent une activité plus grande *in vitro* que celle des tissus des sujets-témoins normaux.

Les fibroblastes sont affectés par la tuberculine à un degré beaucoup plus faible que ne le sont les macrophages et, dans certains cas, ils semblent plutôt stimulés qu'inhibés.

Le caractère du milieu de culture peut modifier l'effet d'inhibition caractéristique de la tuberculine incorporée aux cultures de tissus.

Acknowledgments

The authors are deeply indebted to Dr. Philip R. White for his aid in setting up the tissue culture method and to Dr. John Hanks for his advice and suggestions.

REFERENCES

(1) Rich, A. R., and Lewis, M. R.: The nature of allergy in tuberculosis as revealed by tissue culture studies, Bull. Johns Hopkins Hosp., 1932, *50*, 115.

(2) Aronson, J. D.: Tissue culture studies on the relation of the tuberculin reaction to anaphylaxis and the Arthus phenomenon, J. Immunol., 1933, *25*, 1.

(3) Moen, J. K., and Swift, H. F.: Tissue culture studies on bacterial hypersensitivity: I. Tuberculin-sensitive tissues, J. Exper. Med., 1936, *64*, 339.

(4) Heilman, D. H., Feldman, W. H., and Mann, F. C.: Specific cytotoxic action of tuberculin: Quantitative studies on tissue cultures, Am. Rev. Tubere., 1944, *50*, 344.

(5) Buckley, J. J., Buckley, S. M., and Keeve, M. L.: Tissue culture studies on liver cells of tuberculin sensitized animals in the presence of tuberculin (purified protein derivative), Bull. Johns Hopkins Hosp., 1951, *89*, 303.

(6) Baldridge, G. D., and Kligman, A. M.: The nature of the tuberculin reaction: Failure to demonstrate *in vitro* cytotoxicity of tuberculin for the cells of sensitized animals, Am. Rev. Tubere., 1951, *63*, 674.

(7) Lasfargues, E., Boquet, P., and Delaunay, A.: Cultures de tissus appliquées à la solution de problèmes immunologiques, Ann. Inst. Past., 1947, *73*, 169.

(8) Juhasz-Schäffer, A.: Tuberkuloseimmunität im Lichte der Gewebezüchtungen "*in vitro*", Ztschr. f. Immunitätsforsch. u. exper. Therap., 1928, *56*, 377.

(9) Fischer, A.: Gewebezüchtung. 3 Ausgabe, R. Müller und Steinicke, München, 1930.

(10) Kallós, P.: Beiträge zur Immunbiologie der Tuberkulose, A. B. Hasse, W. Tullbergs Verl., Stockholm, 1941.

(11) Holst, P. M.: Studies on the effects of tuberculin, Tubercle, 1922, *3*, 249, 289, 337.

(12) Favour, C. B., Fremont-Smith, P., and Miller, J. M.: Factors affecting the *in vitro* cytolysis of white blood cells by tuberculin, Am. Rev. Tubere., 1949, *60*, 212.

(13) Witte, S.: Morphologische und serologische Studien über Tuberkulinwirkungen an Leukocyten *in vitro*, Beitr. z. Klin. Tuberk., 1950, *104*, 252.

(14) Wesslén, T.: *In vitro* studies on tuberculin hypersensitivity of lymph cells, Acta dermat.-venereol., 1952, *32*, 195.

(15) Miller, J. M., Favour, C. B., Wilson, B. A., and Umbarger, M. A.: A plasma factor responsible for *in vitro* lysis of leucocytes by tuberculoprotein, Proc. Soc. Exper. Biol. & Med., 1949, *70*, 738.

(16) Miller, J. M., and Favour, C. B.: The lymphocytic origin of a plasma factor responsible for hypersensitivity *in vitro* of tuberculin type, J. Exper. Med., 1951, *93*, 1.

(17) Miller, J. M., Vaughan, J. H., and Favour, C. B.: The role of complement in the lysis of leukocytes by tuberculoprotein, Proc. Soc. Exper. Biol. & Med., 1949, *71*, 592.

(18) Chaussinand, R.: Une nouvelle réaction d'allergie dans la tuberculose, Ann. Inst. Past., 1947, *73*, 811.
(19) Favour, C. B.: Lytic effect of bacterial products on lymphocytes of tuberculous animals, Proc. Soc. Exper. Biol. & Med., 1947, *65*, 269.
(20) Waksman, B. H., and Bocking, D.: Unpublished data, 1952.
(21) Fabrizio, A. M.: Effect of purified fractions of tuberculin on leukocytes from normal and tuberculous animals in tissue cultures, Am. Rev. Tubere., 1952, *65*, 250.
(22) Middlebrook, G.: A hemolytic modification of the hemagglutination test for antibodies against tubercle bacillus antigens, J. Clin. Investigation, 1950, *29*, 1480.
(23) Waksman, B. H.: Specific white cell lysis produced by combination of rabbit antiserum to purified protein (ovalbumin, bovine gamma globulin) with homologous antigen: The role of non-precipitating antibody, J. Immunol., 1953, *70*, 331.
(24) Squier, T. L., and Lee, H. J.: Lysis *in vitro* of sensitized leucocytes by ragweed antigen, J. Allergy, 1947, *18*, 156.
(25) Lurie, M. B.: Studies on the mechanism of immunity in tuberculosis: The fate of tubercle bacilli ingested by mononuclear phagocytes derived from normal and immunized animals, J. Exper. Med., 1942, *75*, 247.
(26) Chase, M. W.: The cellular transfer of cutaneous hypersensitivity to tuberculin, Proc. Soc. Exper. Biol. & Med., 1945, *59*, 134.
(27) Wesslén, T.: Passive transfer of tuberculin hypersensitivity by viable lymphocytes from the thoracic duct, Acta tubere. Scandinav., 1952, *26*, 38.

BRONCHOGRAPHY WITH A WATER-SOLUBLE CONTRAST MEDIUM (UMBRADIL)[1]

SOL KATZ, PATRICK B. STOREY, GEORGES F. McCORMICK, HECTOR PALACIOS, AND ANGEL DeLEON PENSO

(Received for publication April 27, 1953)

INTRODUCTION

Bronchography is acknowledged to be valuable in the diagnosis of diseases of the tracheobronchial tree. It has few contraindications and rarely causes complications. Iodized poppyseed oil is usually employed as the contrast medium. It is safe, nonirritating, and provides excellent contrast visualization of the tracheobronchial tree. However, the retention of this medium in the alveoli and bronchioles interferes with subsequent roentgenographic interpretation of tuberculous lesions. Because of this major disadvantage, a search has been made for a water-soluble contrast material which would disappear rapidly from the lungs.

Morales and Heiwinkel (1, 2) recommended the use of a water-soluble contrast medium called "Umbradil-Viskos B".[2] It is an aqueous solution containing 50 per cent Umbradil (diethanolamine of 3,5-diiodo-4-pyridone-N-acetic acid) rendered viscous by the addition of 2.7 per cent carboxymethylcellulose. It also contains 0.5 per cent xylocaine for local anesthetic effect. Later, a similar medium was developed in Switzerland known as Joduron B (3). In the United States, Diodrast has been used in combination with pure methylcellulose for the same purpose (4). Studies have indicated that these materials are safe (5, 6) and produce reactions in the lung which are reversible.

During the past eighteen months, viscous Umbradil has been used as the bronchographic medium in some of the patients in the Pulmonary Disease Division at Gallinger Municipal Hospital. It is the purpose here to report the results in 45 of these cases.

METHOD

In the preparation for bronchography, patients were given codeine, atropine, and Nembutal. The nostril, oropharynx, and larynx were sprayed with 1 per cent Pontocaine. A rubber catheter was then introduced through the nostril into the trachea. With the onset of cough, 3 cc. of 0.33 per cent Pontocaine were introduced through the catheter. The cough practically always disappeared in less than a minute. An additional 3 cc. of 0.33 per cent Pontocaine were instilled. Cough occasionally recurred but was of short duration. The patient was then fluoroscoped and the tip of the catheter fixed above the level of the carina. A third instillation of 3 cc. of 0.33 per cent Pontocaine was given, which usually elicited

[1] From the Pulmonary Disease Division, Gallinger Municipal Hospital; Department of Medicine, Georgetown University School of Medicine; and George Washington Medical School, Washington, D. C.

[2] The Umbradil used was supplied by Mr. Borje Jalar of the Astra Pharmaceutical Products, Inc., Worcester, Massachusetts.

minimal or no involuntary cough. The patient was then asked to cough in order to clear the tracheobronchial tree.

Although this technique of anesthesia has proved satisfactory for bronchography, using oil contrast media (Iodochlorol, Lipiodol), it was completely inadequate when Umbradil was used. Intractable coughing often occurred before the instillation was complete. Warming the Umbradil or increasing the concentration of Pontocaine often did not help.

Accordingly, the technique was modified by attempting precise fractionated instillation of Pontocaine into the lobar and segmental orifices, thereby permitting unilateral or unilobar bronchography. After the introduction of the catheter into the trachea and the first instillation of 0.33 per cent Pontocaine, the patient was fluoroscoped and the tip of the catheter was guided into the desired main-stem bronchus and anchored in position. Bronchial anesthesia was performed by fractional instillation of 0.33 per cent Pontocaine into the lobar and segmental orifices by placing the patient in the same postures to be employed for the subsequent bronchogram.

Several minutes after the completion of the anesthesia, the Umbradil was introduced slowly as the patient's position was carefully altered to permit visualization of only the desired (anesthetized) segments. It was found that overflow of Umbradil into the other lung must be avoided because uncontrollable coughing will ensue. Moreover, the films must be exposed in quick succession because of the rapid absorption of the water-soluble contrast medium.

RESULTS

Forty-five patients had bronchograms attempted with the use of Umbradil. Ten of these patients coughed so severely that exposure of films was precluded. These patients subsequently had bronchograms made without difficulty, using oily contrast medium.

In the remaining 35 patients, films were made which were of varying quality. Six (17 per cent) had bronchograms which were graded as excellent because they could be considered to be as good as bronchograms made with oily contrast substances. Nine (26 per cent) had bronchograms which could be considered as fair in that they were adequate for diagnostic purposes but not as good as oily contrast medium bronchograms.

Thus, 15 patients (43 per cent) had usable bronchograms in that the desired information was obtained and the procedure did not have to be repeated.

It must be emphasized that, even though adequate bronchograms were obtained in these patients, in some only by maximal cooperation and exercise of extreme will power was coughing suppressed sufficiently to permit exposure of the films. In 20 patients (57 per cent) the bronchograms were inadequate for diagnosis, requiring repeated studies with conventional contrast materials.

REPORTS OF CASES

A satisfactory bronchogram should outline all of the pulmonary segments, and show good contrast. Coughing interferes with these objectives and must not occur.

A normal complete bronchogram made with Iodochlorol is shown in figure 1*A*. The entire tracheobronchial tree is filled. By utilizing both anterior oblique views, the segmental anatomy of both lungs can be visualized. This is standard bronchographic procedure at this hospital.

An Iodochlorol bronchogram of a patient with extensive saccular bronchiectasis is shown in figure 1*B*. Illustrative bronchograms may be seen in figures 2 through 7.

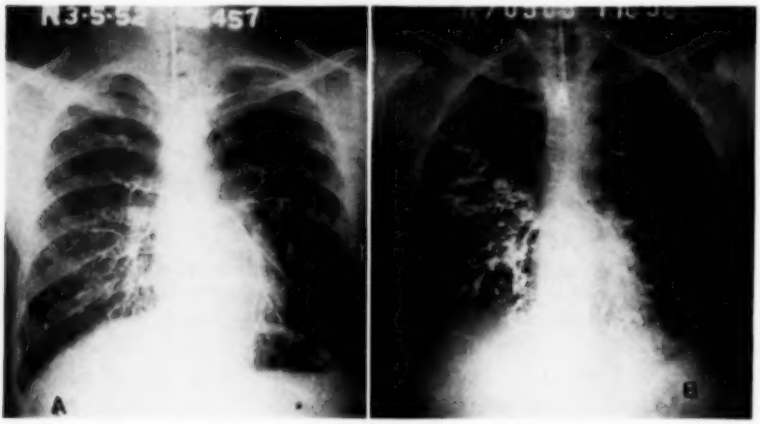


FIG. 1*A*. Normal bronchogram made with Iodochlorol, outlining entire tracheobronchial tree.

FIG. 1*B*. Bronchogram made with Iodochlorol, showing extensive bilateral saccular bronchiectasis.

DISCUSSION

The present results should not be construed as a complete condemnation of Umbradil for bronchography. It is indeed a useful material in selected cases in which limited (lobar) bronchography suffices and retention of a contrast medium in the lung is especially undesirable. This latter situation is an important consideration in the management of tuberculosis when proper interpretation of changes in roentgenograms may be made difficult because of a residual contrast substance. However, when a complete mapping of a lung or of both lungs is necessary, Umbradil is not suitable because it is so severely irritating that safe, satisfactory anesthesia cannot be accomplished to permit its use.

Work done by others is pertinent to this discussion. Morales (2) expressed enthusiasm for Umbradil, but it should be noted that in his report very limited bronchograms were obtained using fluoroscopic control and a spot film technique. The results of the present study, therefore, do not contradict his opinion but actually are in agreement with it. Poppe and Odegaard (7) were pleased with their results with Umbradil. They mentioned, however, that Umbradil was more irritating than oily media; that more extensive and tedious anesthesia was necessary; that bronchography with Umbradil was more time consuming; that only one lung could be outlined at one sitting; and that they hoped that a better water-soluble medium would soon be available. In their report they emphasized that the roentgenograms should be taken as spot films on a tilting fluoroscopic

table and that the exposures must be made quickly, not only because of rapid absorption of the contrast substance, but also because of the cough which develops after the injection. In spite of their satisfaction with Umbradil, it is apparent that they recognized definite limitations in its use. Brandenstein (8), using Ioduron B, showed bronchograms which would not be considered completely satisfactory. Jones (9) was disappointed in the medium because it was so irritating and had inadequate contrast properties. However, objection might be raised against his conclusions because he did not use adequate prebronchographic medication or sufficient local anesthesia.

In evaluation of a study of the type of the present report, many variables must be considered. There is variation in the skill of the operators and variation in bronchographic technique. Moreover, there are distinct differences in what is expected of a bronchographic study. Using experience in this clinic with oily contrast substances as a basis for comparison, Umbradil has not proved to be as good as oily contrast materials. However, because of its rapid absorption from the lung, it has a place in bronchography in selected cases.

SUMMARY

Bronchography with a water-soluble contrast medium (Umbradil) is more difficult than with oily contrast substances because of the irritant nature of Umbradil.

However, because of its rapid absorption from the lung, it has a useful place in selected cases in which limited (lobar) bronchography suffices and in which retention of a contrast medium in the lung is especially undesirable.

SUMARIO

La Broncografía con Medios Hidrosolubles de Contraste (Umbradil)

La broncografía con Umbradil es más difícil que con substancias oleosas de contraste, a causa de la naturaleza irritante de dicho medio.

Sin embargo, debido a su rápida absorción en los pulmones, tiene su puesto útil en casos seleccionados en los que basta con una broncografía limitada (lobular) y en los que resulta en particular inconveniente la retención de un medio de contraste en el pulmón.

RESUME

Bronchographie avec un milieu de contraste soluble dans l'eau (Umbradil)

La bronchographie à l'aide de l'Umbradil est plus difficile à exécuter qu'avec les substances de contraste huileuses en raison de la nature irritante de l'Umbradil.

L'absorption rapide de cette préparation au niveau du poumon permet de l'utiliser avec profit dans des cas sélectionnés ne nécessitant qu'une bronchographie limitée (lobaire) et dans lesquels la rétention d'un milieu de contraste au niveau du poumon est particulièrement indésirable.

REFERENCES

(1) Morales, O., and Heiwinkel, H.: A viscous, water-soluble contrast preparation: Preliminary report, Acta radiol., 1948, *30*, 257.

(2) Morales, O.: Further studies with viscous Umbradil (Umbradil-Viskos): Its indications and technical application, Acta radiol., 1949, *32*, 317.

(3) Fischer, F. K.: Technik, Indikationen und Ergebnisse der Bronchographie mit wasserlöslichem viskosem Kontrastmittel (Joduron "B"), Schweiz. med. Wchnschr., 1950, *80*, 723.

(4) Peck, M. E., Neerken, A. J., and Salzman, E.: Clinical and experimental studies in the use of a water-soluble agent for bronchography, Surg., Gynec. & Obst., 1951, *92*, 685.

(5) Hellstrom, B., and Holmgren, H.: Reaction of the lung on bronchography with viscous Umbradil (Umbradil-Viskos B) (Astra), Umbradil (Astra), and carboxymethyl cellulose: Experimental investigation on animals, Acta radiol., 1949, *32*, 471.

(6) Vischer, W.: Veranderungen des Lungengewebes nach Bronchographie mit Joduron B, Schweiz. med. Wchnschr., 1951, *81*, 54.

(7) Poppe, K., and Odegaard, H.: Bronchography with water-soluble contrast medium, Radiology, 1952, *59*, 831.

(8) Brandenstein, L. C.: Ioduron B. Bronchography: Preliminary report of study with water-soluble contrast medium, Am. J. Roentgenol., 1951, *66*, 769.

(9) Jones, S. J.: A new contrast medium for bronchography with a comparison of iodised oils and Umbradil Viscous B, Brit. J. Tubere., 1952, *46*, 168.

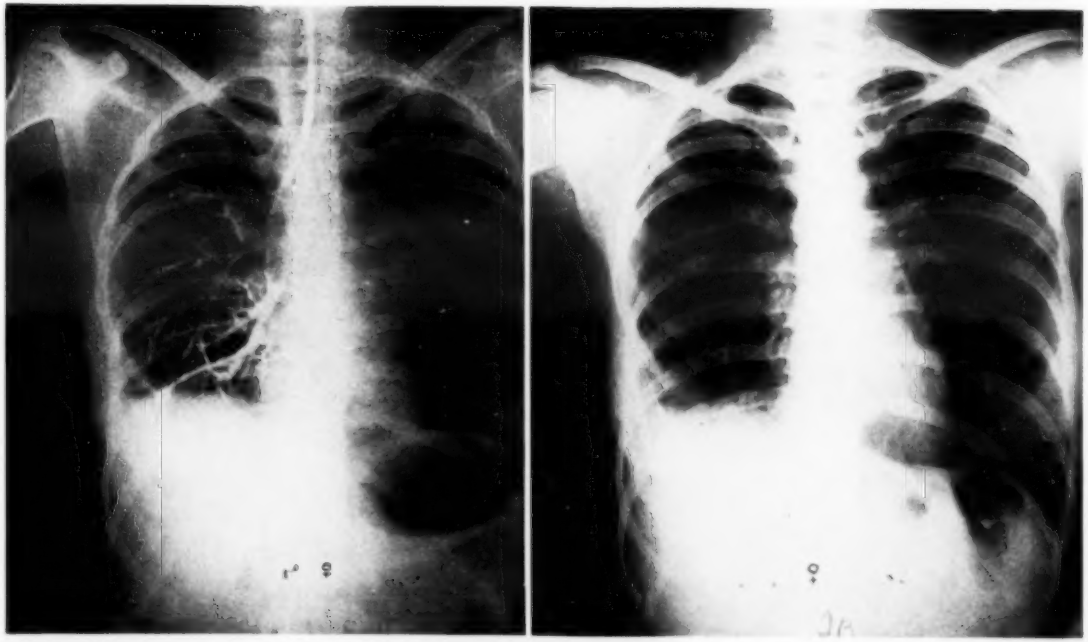


FIG. 2. *Case 1.* A young woman had a right lower lobe lobectomy for tuberculosis five years previously. Subsequently, she developed symptoms suggestive of reactivation of her disease. Following therapy there were a remission of her symptoms, cavity closure, and practically complete clearing of the lesion.

(Left). A bronchogram was done with Umbradil because of the suspected presence of middle lobe bronchiectasis. Note that the catheter is in the right main-stem bronchus. No attempt was made to outline the bronchi on the left side. During the procedure the patient struggled in order not to cough and was successful. The bronchographic result was excellent, illustrating bronchiectasis of the right middle lobe.

(Right). Twenty-four hours later, a repeat roentgenogram showed no trace of retained Umbradil.

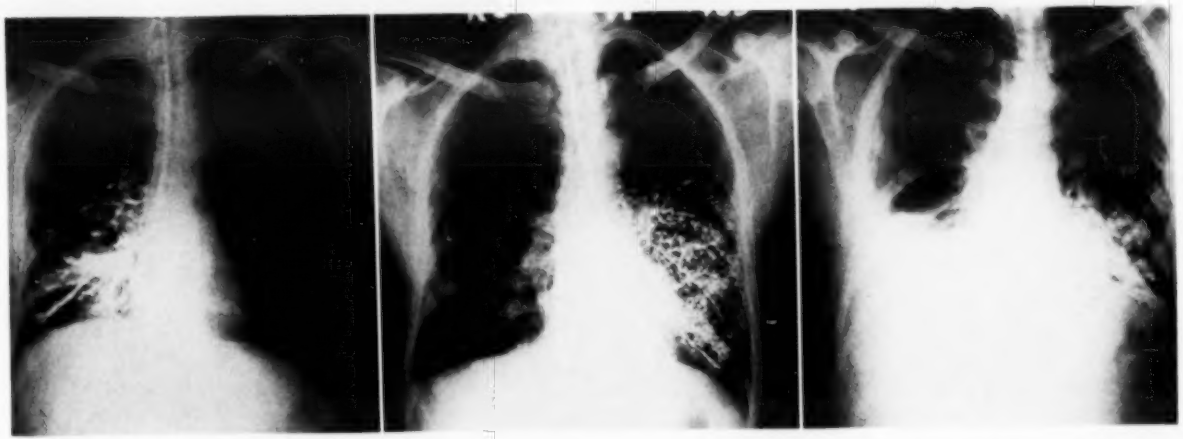


FIG. 3. *Case 2.* A middle-aged Negro male with symptoms of chronic bronchopulmonary disease was thought to have chronic lung abscess and bronchiectasis.

(Left). Right-sided bronchogram, performed with Umbradil, illustrated a large cavity in the dorsal division of the right lower lobe with bronchiectasis of the basal segments. The patient had no difficulty tolerating the procedure. (Center). Two weeks later the left lung was outlined with Iodochlorol. There is no trace of Umbradil in the right lung and the outline of the cavity can be seen.

(Right). Five days later the right lower lobe was resected. The dense smudging from retained Iodochlorol can be seen in the left lung. This case serves to illustrate the major advantage of Umbradil and the major disadvantage of oily contrast medium.

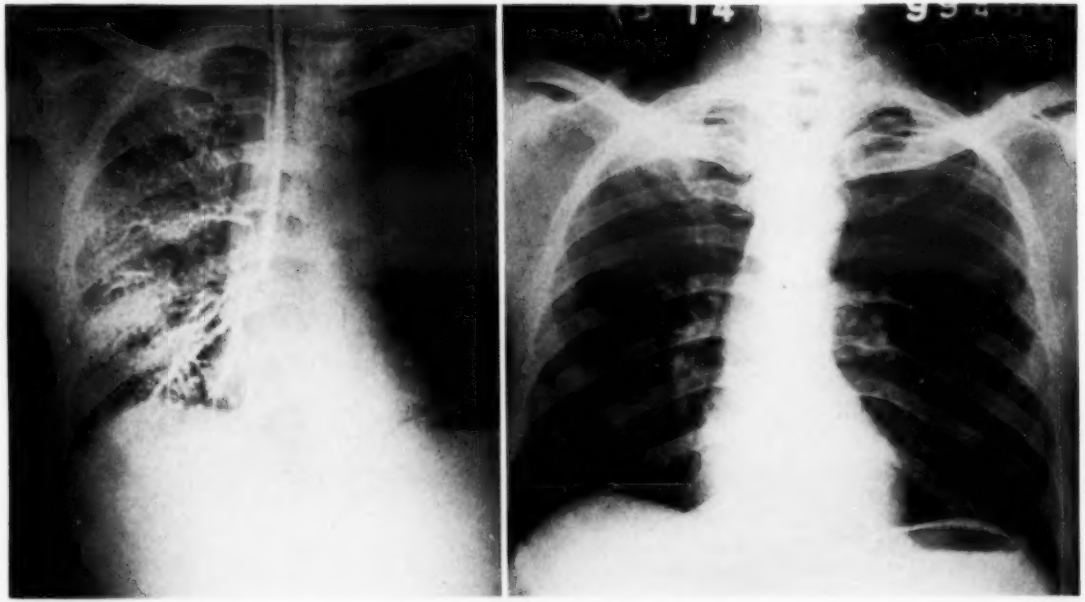


FIG. 4. *Case 3.* A patient with pulmonary tuberculosis had suspected bronchiectasis of right upper lobe.

(Left). Bronchogram of right lung made with Umbradil. Note catheter in right bronchus intermedius. There was no attempt to outline the left side. Patient tolerated the procedure well and did not cough. The result was excellent.

(Right). A repeat film one hour later showed complete clearing of the Umbradil.

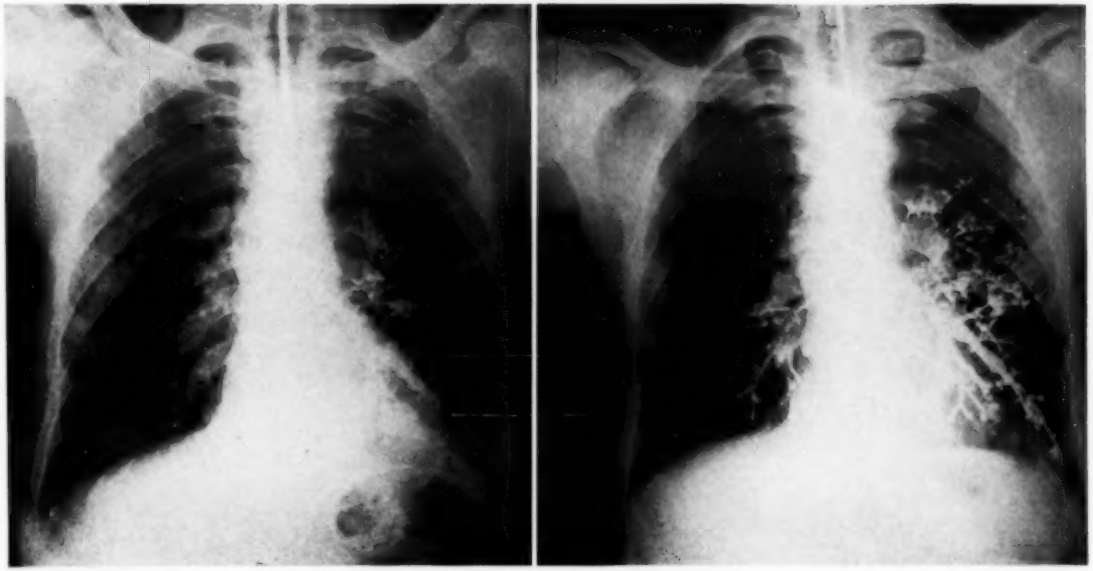


FIG. 3. *Case 4.* A middle-aged Negro male was admitted with symptoms of acute lower respiratory infection and was found to have a giant cyst in the lower left lung field. Symptoms responded to antimicrobial treatment and the cyst disappeared from view.

(Left). Bronchogram made with Umbradil suggested the presence of bronchiectasis, but is of poor contrast quality. However, sufficient detail was not obtained.

(Right). The procedure was repeated three weeks later, using Iodochlorol. No attempt was made to fill the right side. It clearly demonstrated extensive bronchiectasis. This patient did not cough.

FIG. 6. *Case 5.* A middle-aged Negro male had chronic bilateral far advanced pulmonary tuberculosis. Patient also has a pneumoperitoneum.

(Left). Bilateral bronchogram was attempted with Umbradil, but coughing could not be controlled.

(Right). Subsequently, the procedure was carried out successfully and without difficulty, using Iodochlorol.

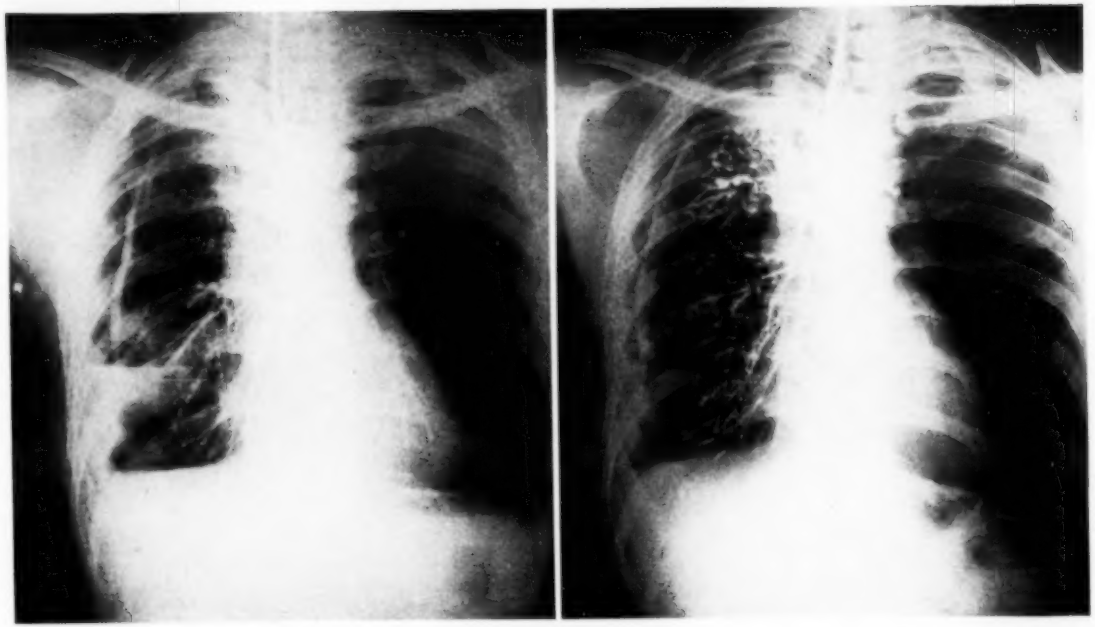


FIG. 7. *Case 6.* A middle-aged Negro male had chronic empyema and bronchopleural fistula secondary to pulmonary tuberculosis.

(Left). Right-sided bronchogram with Umbradil was unsuccessful.

(Right). A repeat bronchogram, using Iodochlorol, was easily accomplished and showed a retracted, bronchiectatic right upper lobe.

Case Reports

CARDIAC INVOLVEMENT IN MILIARY TUBERCULOSIS[1]

HSIANG-LEN TSENG AND F. ROULET

(Received for publication April 17, 1953)

INTRODUCTION

Tuberculosis of the heart, including miliary tuberculosis, solitary tubercules, and diffuse tuberculous myocarditis, has been reported from time to time although it is still a rare finding. The involvement of coronary vessels by tuberculous processes is even more so. It was first reported by Wätjen (1), Brockhausen (2), Goulet and his associates, (3) and Alphonse (4) subsequently reported tuberculosis of the myocardium with cellular infiltration, endophlebitis, and even caseation. Recently, Waser (5) described a case of miliary tuberculosis of the aorta showing separated individual thrombus-like tubercles surrounded by endothelial cells which showed either disintegration or swelling. Thrombosis of the coronary vessels due to tuberculosis has been described only once, by Lieberweiser in 1909 (6). Because of the rarity of the above-mentioned conditions, the following case is reported.

CASE REPORT

Case Report Autopsy No. 183/48. The patient was a thirty-year-old married woman who had an attack of angina in 1947, followed by frequent palpitation. One of her brothers died of heart disease at the age of twenty-five. Fourteen days before admission to the hospital she had fever, difficulty in breathing, and headache. The attending physician found that she had miliary tuberculosis with signs of meningitis, renal disease, and an eight-month pregnancy. Streptomycin was given both intramuscularly and intrathecally and she was admitted to Basel Lying-in Hospital on February 12, 1948, for caesarean section, which was performed the next day. A normal well-developed male infant weighing 2,240 gm. was delivered. In the hospital her temperature fluctuated between 98.6° and 103°F. and the pulse was approximately 130 per minute and regular. Blood pressure varied from 140 systolic and 80 diastolic in mm. of mercury at the time of admission to 120 systolic and 75 diastolic two days later. Electrocardiographic tracing showed a deep S wave in lead I and CF4, depression of ST segment in lead II, lead III, and CF4, and inverted T wave in lead III. The interpretation of the electrocardiogram was sinus tachycardia and myocardial damage. Examination of the ocular fundi revealed engorgement of the retinal vessels and papilledema of the right side. A roentgenogram of the chest confirmed the diagnosis of miliary tuberculosis. Two cerebrospinal fluid examinations showed an increase of leukocytes, 180 and 210 per cu. mm., respectively, and also an increase of protein content to 0.3 gm. per 100 ml. There was a leukocytosis of 15,000 per cu. mm. in the peripheral blood two days before death, while the initial count was within normal limits. The urine contained one-plus protein, a few erythrocytes and leukocytes, but no casts. Tubercle bacilli were not found in the sputum or cerebrospinal fluid. Blood urea and nonprotein nitrogen were 33 and 50 mg. per 100 ml., respectively. Despite continuous administration of streptomycin and supportive treatment, the patient became increasingly cyanotic and dyspneic and gradually went into coma. She died three days after operation with respiratory failure.

[1] From the Illinois Masonic Hospital, Chicago, Illinois, and the Department of Pathology of Basel University Medical School, Switzerland.

Post-mortem examination: The autopsy was performed twenty-two hours after death. Macroscopic diagnoses were subacute miliary tuberculosis of both lungs, liver, spleen, thyroid gland, and peritoneum, residual caseous tuberculosis of the bronchial and tracheal lymph nodes, tuberculous meningitis, thrombosis of uterine veins, edema of the brain, and slight, diffuse colloid goiter. No emboli were seen in the pulmonary vessels.

The *heart* grossly was not enlarged, and weighed only 245 gm. It was flabby with dilatation of all chambers. All of the valves were normal and the foramen ovale was closed. The left ventricle was normal in thickness and, on section, the myocardium appeared rather pale and brown in color. In the anterior wall of the left ventricle was a white patch approximately 0.5 cm. in diameter with a rather irregular outline. The immediate surrounding area was dull red. The coronary arteries were free from atherosclerosis. Both the pericardium and the endocardium were normal.

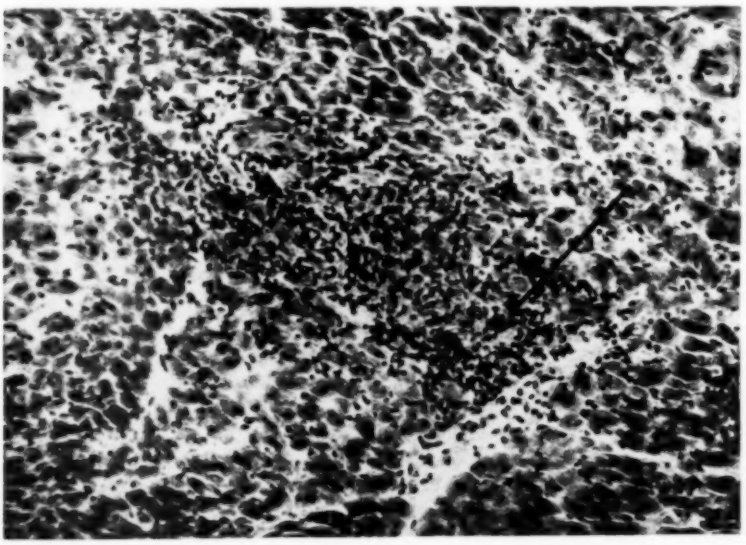


FIG. 1. Section of left ventricle showing tubercle in myocardium with Langhans' giant cell (arrow pointed). Hematoxylin-eosin stain (×160).

Microscopic examination: Microscopic examination, besides confirming the macroscopic diagnoses, revealed miliary tubercles in the left ventricle, involving the anterior wall, apex, and the septum, while the right ventricle was free (figure 1). There were epithelioid cells, more in the center of the tubercles, intermingled with and surrounded by lymphocytes. A few polymorphonuclear leukocytes were also seen in the periphery of the tubercles. Giant cells of Langhans' type were found in the septum only. Nowhere was there any caseation. In addition, there were marked myocardial fragmentation and brown atrophy. Fatty infiltration of myocardial fibers was seen in the form of globules, more marked in the right ventricle and especially around the large vessels. In the septum there was fine droplet fatty degeneration, especially toward the endocardium and epicardium. In some places in the anterior wall of the left ventricle, similar fatty degeneration, especially around the tubercles, was noted.

Marked degeneration of the myocardial fibers, with replacement by fibrous tissue, and a few fibroblasts and histiocytes around the vessels were also seen. In the left ventricle,

where the whitish patch was seen grossly, fresh necrotic foci were found and the degenerated and necrotic muscle fibers appeared as short and distorted, or threadlike, fragments. Little of the sarcolemma could be recognized, while the degenerated fibers consisted of fine acidophilic granules. In the necrotic foci (figure 2) many histiocytes, small round cells, and polymorphonuclear leukocytes were seen. Fibrin was also present. A little further from the foci, plasma cells also appeared.

In serial sections, the necrotic foci appeared to arise from thrombosis of small arterioles which caused complete obstruction of the lumen. The media of these vessels showed fibrinoid swelling, and proliferation of the endothelial cells also was found. Weigert's elastic stain showed disintegration and, in places, complete disappearance of the intimal elastic lamina. In the rest of the myocardium there was slight degeneration of muscle fibers with

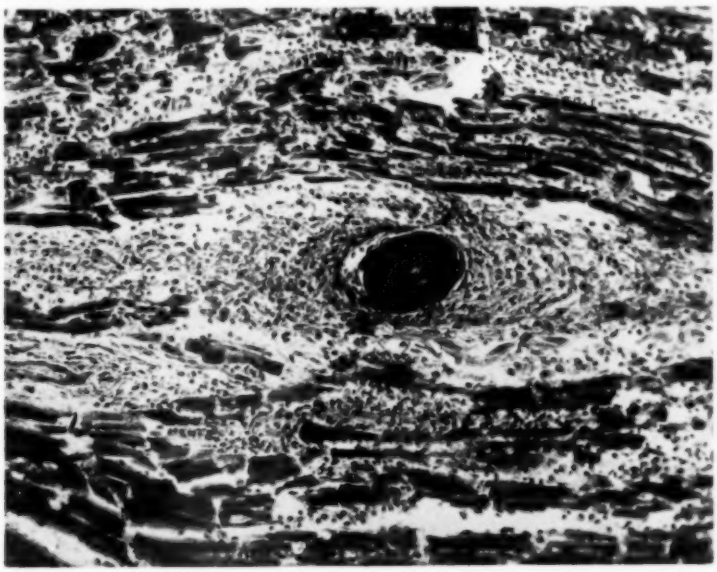


FIG. 2. Section of left ventricle showing occlusion of small artery with necrosis of myocardial fibers and cellular reaction. Hematoxylin-eosin stain (×125).

interstitial infiltration by histiocytes, fibroblasts, a few round cells, and polymorphonuclear leukocytes. Tubercle bacilli were found only in the thrombi on Ziehl-Neelsen staining.

COMMENT

This case presented unquestionable miliary tuberculosis of the heart as shown in figure 1 and, in addition, there was the unusual formation of thrombi in the small coronary arteries with necrosis of the surrounding myocardial fibers and inflammatory cellular reactions. The possibility of emboli coming from the thrombi of the uterine plexus can be excluded by the closed foramen ovale and the absence of emboli in the pulmonary vessels.

Koch (7), in a general review of the pathogenesis and pathology of tuberculous leptomeningitis, had mentioned changes in the vessels. In the larger arteries he found changes in the intima and adventitia with fibrinoid swelling and cellular proliferation but the

media was apparently not unusual. The cellular accumulation was slight in the intima but there were flakes or fine basophilic staining masses, apparently leading to cushion-like thickening. In some places the endothelial cells were somewhat swollen and protruded into the lumen of the vessels. In the smaller arteries, all three layers were involved in a homogenous mass which stained yellow with van Gieson's stain in the intima. The change in the adventitia was the same as that of the larger arteries. The proliferation of the cells assumed many forms and Koch speaks of a term suggested by Siegmund, "budding condition of mesenchyma," which together with the fibrinoid swelling were the two major changes in the vessels.

With the aid of special stains for elastic fibers and fibrin, the present writers found fibrinoid swelling of the media, disintegration of the intima with partial disappearance of the internal elastic membrane, and some proliferation of the endothelium, similar to the changes described by Koch. It is believed that there are first pathologic changes in the vessels as described above, followed by formation of thrombi by the deposit of platelets, blood corpuscles, and tubercle bacilli, in the same way that thrombi are formed in inflamed or injured vessels in other parts of the body. Gradually, the thrombi become larger and, finally, complete occlusion of the lumen occurs, resulting in focal necrosis of myocardial fibers and inflammatory cellular reactions.

SUMMARY

A case of miliary tuberculosis with involvement of the heart is reported. Changes of small coronary vessels followed by thrombus formation resulting in necrosis and cellular inflammatory reaction are presented.

SUMARIO

Invasión Cardiaca en la Granulia

Preséntase un caso de granulia con invasión del corazón. Descríbense las alteraciones observadas en los pequeños vasos coronarios, seguidas de trombosis, dando por resultado necrosis y reacción inflamatoria en las células.

RESUME

Lésion cardiaque dans la tuberculose miliaire

Un cas de tuberculose avec lésion du coeur est rapporté.

Présentation d'une observation montrant des altérations des petits vaisseaux coronaires dues à la formation d'un thrombus avec nécrose et réaction inflammatoire secondaires.

REFERENCES

(1) Wätjen: quoted from Brockhausen, K. (2).

(2) Brockhausen, K.: Herztuberculose, Virchows Arch. f. path., 1930, *274*, 302.

(3) Goulet, B. A., Bellet, S., and McMillan, T. M.: Tuberculosis of the myocardium, Arch. Int. Med., 1933, *51*, 244.

(4) Alphonse, P.: La tuberculose du coeur; la phlebite tuberculeuse du myocarde, Verhandlungen d. Schweiz. Med. Biol. Gesellsch., 1941.

(5) Waser, P.: Die miliare aortentuberculose, Schwerz. Ztschr. f. Path. u. Bakt, 1948, *11*, 29.

(6) Lieberweiser, G.: Studien uber Komplikationen der Lungentuberculose un uber die Verbreitung der Tuberkelbazillen im den Organen und im Blut der Phthisiker, Virchows Arch. f. Path., 1909, *197*, 332.

(7) Koch, O.: Beitrage zur allgemeinen Pathogenese und Pathohistologie der tuberculosen Leptomeningitis, Beitr. z. Klin. Tuberk., Verlage von Julius Springer, 1940.

MECHANISM OF MEDIASTINAL EMPHYSEMA COMPLICATING THERAPEUTIC PNEUMOPERITONEUM[1]

J. WINTHROP PEABODY, JR. AND HOWARD A. BUECHNER

(Received for publication April 27, 1953)

INTRODUCTION

Largely as a result of clinical studies by Hamman (1–5) and laboratory investigations by the Macklins (6–9), mediastinal emphysema, both as a primary disease (spontaneous mediastinal emphysema) and as a complication of other conditions, has become so well established a clinical entity that further generalizations on the subject seem pointless. The available anatomic routes by which air may gain access to the mediastinum have been reduced to four: viz., perforation directly into the mediastinum from the trachea, bronchi, and esophagus; rupture of alveoli into the pulmonary interstitial tissue with dissection of air along the perivascular and peribronchial sheaths into the mediastinum; dissection of air into the mediastinum from the deep fascial planes of the neck; and dissection of air into the mediastinum from the retroperitoneal space. In all but one form of pneumomediastinum, these pathways appear applicable. For that secondary to therapeutic pneumoperitoneum, however, no route has gained general acceptance, which suggests that a fifth pathway must be available. While most attempts to explain this complication have been based, not upon sound anatomic principles, but upon hypothetical defects in, or rupture through, the normal anatomy, the experiences of the present writers indicate that in some cases, at least, this aberrant air does traverse normal and easily discernible anatomic planes.

It has been possible to collect from the literature only thirty-four cases of mediastinal emphysema subsequent to artificial pneumoperitoneum (10–22); yet it must not be an uncommon experience, judging by a report of ten cases at one hospital during a fourteen-month period (10).

At this hospital two such cases have been encountered in the course of some 4,000 refills during the past twenty-four months. In both of these cases, as well as in the majority of those described in the literature, mediastinal emphysema occurred following a refill rather than at the time of induction, and more often than not the pneumoperitoneum was resumed without ill effect. Findings such as these argue strongly against the possibility of an underlying congenital diaphragmatic defect or an acquired diaphragmatic tear, either of which would seem incompatible with further therapy. Introduction of air directly into the mesentery of the bowel would afford entry to the retroperitoneal space, but the likelihood of such an occurrence should be extremely small with the patient on his back and a broad expanse of air between the parietal peritoneum and the bowel. Therefore, most writers have found it necessary to postulate a rupture of air through an area of peritoneal weakness into the retroperitoneal space. Evidence in support of this contention appears to be almost completely lacking, however. While admitting that a rare case may develop in this fashion, the present writers are convinced that a much more valid explanation is available.

Banyai and Jurgens (12) have proposed a mechanism which may be applicable to cases in which a subcostal approach is utilized, namely, the introduction of the needle between

[1] From the Tuberculosis Service of the Veterans Administration Hospital, New Orleans, Louisiana.

the diaphragmatic pleura and the diaphragm, thus permitting air to travel between these two layers over the superior diaphragmatic surface into the mediastinum. Because they encountered mediastinal emphysema only with the subcostal site of puncture, these writers believe that most cases arise in this manner. On the basis of the present writers' experience, such precise placement of the needle point hardly appears necessary to explain this phenomenon, for the anterior abdominal wall affords a ready avenue of approach to the mediastinum. This has been previously pointed out by Weiss and Stanley (19) and is further substantiated by the following case report.

CASE REPORT

A 30-year-old white male attorney was admitted to the hospital on July 10, 1951, with a diagnosis of active pulmonary tuberculosis for which a pneumoperitoneum had previously been instituted elsewhere. Roentgenograms of the chest revealed a diffuse pneumonic infiltration throughout the upper one-third of the right lung, and sputum examinations were repeatedly positive for acid-fast bacilli.

The diagnosis of moderately advanced, active, pulmonary tuberculosis was confirmed, and the patient was placed on a regimen of complete bed rest, streptomycin, and para-aminosalicylic acid. The pneumoperitoneum was maintained. On the above therapy he remained afebrile and asymptomatic and gained 10 pounds in weight. The sputum became negative for tubercle bacilli in August, 1951, and remained so thereafter. Serial roentgenograms of the chest disclosed rapid and dramatic regression of the infiltrative process in the right upper lung, and by October, 1951, only a small focus of predominantly fibrotic disease could be visualized in the right first anterior interspace. Throughout the remainder of the period of observation this lesion continued to undergo gradual contraction and resolution.

Development of mediastinal emphysema: During the patient's hospitalization, pneumoperitoneum refills were carried out at weekly intervals. On November 28, 1951, the eighteenth pneumoperitoneum refill was performed. The needle was introduced into the left upper quadrant of the abdomen, approximately 8 cm. below the left subcostal margin and 7 cm. to the left of the midline. An initial pressure gradient of 4 to 7 cm. of water was obtained with full excursion on respiration. Following introduction of several hundred cubic centimeters of air, the patient began to complain of epigastric and back pain followed by low retrosternal distress. The introduction of air was momentarily halted with complete cessation of pain. However, soon after reinstituting the flow of air, his complaints returned and the pain behind the sternum was described as progressively ascending. The procedure was therefore discontinued following the introduction of a total of 650 cc. of air. The occurrence of mediastinal emphysema was strongly suspected and this was confirmed by the presence of an auscultatory precordial crunch synchronous with the heart beat. An erect postero-anterior roentgenogram of the chest (figure 1) showed a clearly defined mediastinal emphysema, manifested by a linear zone of radiolucency outlining the left border of the heart and, to a lesser extent, the right border of the heart, and extending upward into the paravertebral region of the neck. On the oblique views, radiolucent zones were demonstrable in the superior mediastinum. In the lateral view (figure 2), it was possible to visualize a linear radiolucent shadow extending from the anterior abdominal wall superiorly into the anterior mediastinum. On the basis of the lateral view, it appeared evident that the air had been introduced deep into the abdominal wall, whence it had dissected upward into the mediastinum.

Throughout the remainder of that day, the patient continued to complain of moderate substernal distress and developed a "popping" sensation in the right supraclavicular fossa on turning his head to the right. Still later he complained of slight dysphagia and a "crunching" in both ears when chewing. At no time was subcutaneous emphysema demonstrable in the neck. By the following day, the symptoms of mediastinal emphysema were rapidly subsiding and Hamman's sign was no longer audible. Five days following the occurrence of the mediastinal emphysema, all roentgenographic evidence of air in the mediastinum had

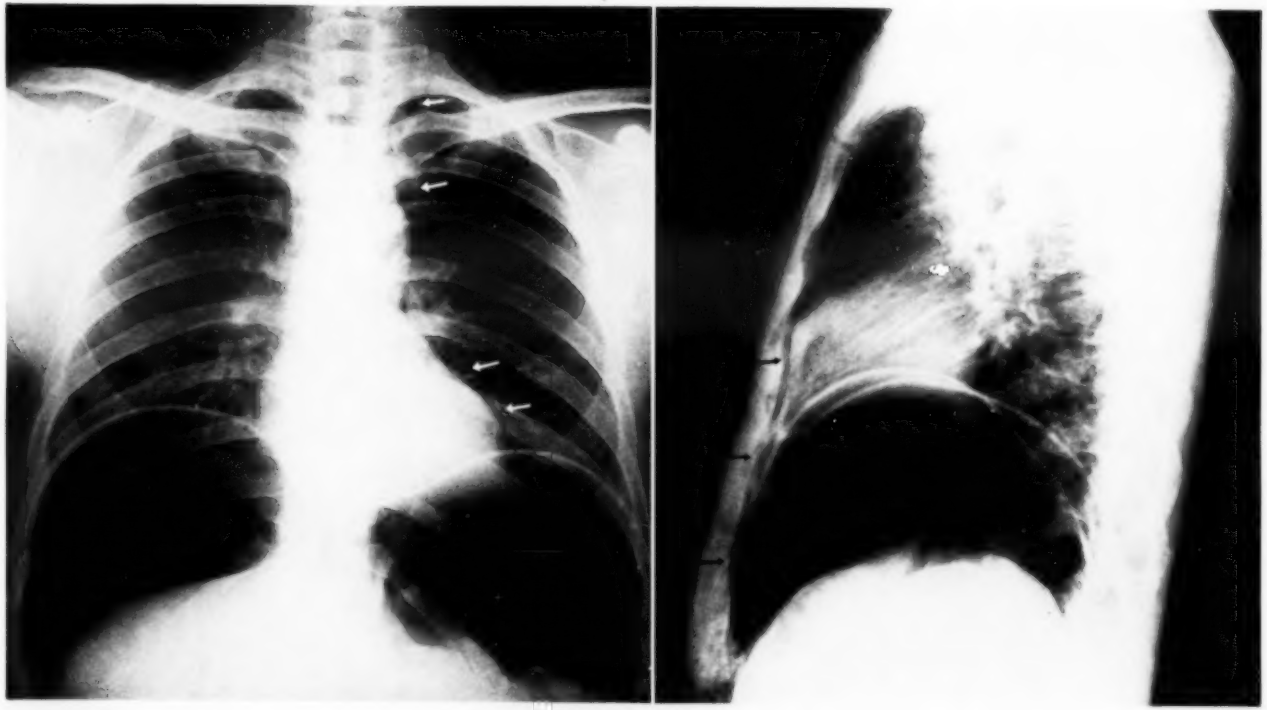


FIG. 1. (Left) Postero-anterior roentgenogram showing mediastinal emphysema outlining the left mediastinal pleura, inferiorly along the left paracardiac area and superiorly above its attachment to the aortic arch. Air is also visualized in the right paravertebral region of the neck.

FIG. 2. (Right) Lateral roentgenogram depicting the linear dissection of air from the approximate point of needle puncture up through the anterior abdominal wall into the mediastinum.

disappeared. Two days later, artificial pneumoperitoneum was reinstituted, 1,000 cc. of air being given without incident. Subsequent periodic refills were likewise uneventful. On January 22, 1953, the patient was discharged from the hospital. During subsequent follow-up studies, the pulmonary lesion continued to regress and at this time only a vague linear streaking is present in the first anterior interspace on the right. The patient is clinically well and has returned to employment. Pneumoperitoneum is still being maintained.

COMMENT

Soon after the experience with mediastinal emphysema in this patient, a similar case[2] came to the attention of the writers in which the lateral roentgenogram of the chest again disclosed a linear radiolucent shadow in the anterior abdominal wall, extending from the approximate level of the needle puncture into the anterior mediastinum.

From a review of the anatomy of the diaphragm in its relation to the anterior abdominal wall, it is quite simple to reconstruct a potential pathway by which aberrant air may reach the mediastinum. Rives and Baker (23) have shown that the diaphragm is continuous with the inner fibromuscular layer of the abdominal wall, that is, the posterior rectus sheath and the transversus abdominis muscles. Introduction of air superficial to this layer places it in a potentially open tissue plane which extends up over the superior surface of the diaphragm where it readily enters the mediastinum. Other possible routes include that along the under surface of the diaphragm through the diaphragmatic hiati when air is placed deep to the transversus abdominis, and that through the foramina of Morgagni (spaces of Larrey) alongside the superior epigastric vessels when air is introduced into the rectus sheath. From an interpretation of the lateral roentgenogram, dissection of air superficial to the fibromuscular layer appears to have been the likely course in this patient.

An attempt was made to delineate these tracts in cadavers by the injection of hydrogen peroxide tinted with methylene blue between the deep layers of the abdominal wall. The left side was arbitrarily selected for injection in all cadavers at a point several centimeters above the umbilicus. Restriction of the injected solution to a particular tissue plane proved impossible, and yet, while no uniform results were observed, some evidence in support of the foregoing contention was obtained.

In four cadavers the injections were made lateral to the rectus sheath, and on three of these occasions hydrogen peroxide was found both superficial and deep to the transversalis aponeurosis. In two of these three cases, bluish froth reached the mediastinum. In the fourth case the injection occurred both into the properitoneal layer and within the peritoneum, but did not go into the mediastinum. Four more cadavers received injections of hydrogen peroxide within the substance of posterior rectus sheath, but in none of these could air bubbles be demonstrated within the mediastinum.

These results, while not altogether conclusive, conform closely to accepted anatomic studies, for injection into the posterior rectus sheath would not be expected to lead to mediastinal emphysema. Within the posterior sheath the transversalis aponeurosis is fused on its anterior surface with the posterior lamella of the internal oblique, thus obliterating the tissue plane that exists superficial to the transversalis aponeurosis lateral to its fusion with the internal oblique. Thus, with introduction of air through the posterior rectus sheath, the only site for its injection other than intraperitoneally is in the properitoneal region which would seem to be a less likely source of mediastinal emphysema. On the other hand, air is more apt to reach the mediastinum when it is injected lateral to the rectus sheath and just superficial to the transversalis aponeurosis or muscle.

Despite the gross inadequacies of these experiments, there is ample evidence to indicate

[2] Case of Dr. John H. Seabury.

that some, and perhaps most, instances of mediastinal emphysema during pneumoperitoneum administration result either from failure to insert the needle completely through the abdominal wall or, if properly inserted, from inadvertent withdrawal of the needle during the administration of air. The first possibility can be obviated by insistence upon free manometric respiratory excursions prior to the introduction of air. That of inadvertent withdrawal, however, will probably occur occasionally despite watchful technique, particularly in persons with a thick abdominal wall in whom an attempt to maintain the stubby, extracutaneous portion of the needle at an exact depth can easily produce a pull on the needle hub sufficient to remove at least a part of the bevel from within the free peritoneal space. It is this chain of events which probably led to mediastinal emphysema in the present case, since free manometric fluctuations were obtained before instituting the flow of air. It is believed that the routine utilization of lateral roentgenograms in cases of mediastinal emphysema complicating pneumoperitoneum will prove that a substantial number stem from this technical error, and that an awareness of this danger will render its occurrence less likely. It is suggested that the less dangerous and preferable site of needle puncture is through the rectus sheath.

SUMMARY

The various anatomic routes which air may traverse in cases of mediastinal emphysema complicating pneumoperitoneum therapy have been reviewed.

The writers have encountered two cases in which air dissected from the site of needle puncture in the anterior abdominal wall into the mediastinum. One of these is reported in detail.

This pathway is demonstrable in lateral roentgenograms of the chest and these should be utilized in every case of similarly induced mediastinal emphysema.

Anatomic studies indicate, and the writers' investigative efforts tend to substantiate, the importance of the fibromuscular layer formed by the continuity between the transversalis muscle and the diaphragm. Injection of air superficial to this layer affords a potential tissue plane through which air can easily dissect over the diaphragm and into the mediastinum.

It is suggested that the preferable site for needle puncture is through the rectus sheath, for here there is no space superficial to the transversalis aponeurosis due to its fusion with the posterior layer of the internal oblique muscle.

SUMARIO

Mecanismo del Enfisema Mediastínico que Complica el Neumoperitoneo Terapéutico

Repásanse aquí las varias vías anatómicas que puede atravesar el aire en los casos en que un enfisema mediastínico complica la neumoperitoneoterapia.

Los AA. han observado 2 casos en los que el aire cruzó los tejidos desde el sitio de la punción de la aguja en la pared anterior del abdomen hasta el mediastino. Uno de ellos es descrito con todo detalle.

Esa vía es observable en las radiografías laterales del tórax, las cuales deben ser utilizadas en todo caso de enfisema mediastínico inducido en forma semejante.

Los estudios anatómicos, y las investigaciones de los AA., parecen confirmar, la importancia de la capa fibromuscular formada por la continuidad entre el músculo transverso y el diafragma. La inyección de aire más arriba de esa capa crea un plano potencial de tejido a través del cual puede abrirse paso fácilmente el aire sobre el diafragma y penetrar en el mediastino.

Apúntase que el sitio preferible para punción con aguja es a través de la vaina de' recto

mayor, por no haber allí ningún espacio que quede en la superficie de la aponeurosis del transverso, dada su fusión con la capa posterior del oblicuo interno del abdomen.

RESUME

Mécanisme de l'emphysème médiastinal, complication du pneumopéritoine thérapeutique

Examen des diverses voies anatomiques qui peuvent être empruntées par l'air dans le cas d'emphysème, séquelle de la création d'un pneumopéritoine thérapeutique.

Les auteurs ont rencontré deux cas dans lesquels l'air s'échappait dans le médiastin à partir du siège de la ponction, au niveau de la paroi abdominale antérieure. Un de ces cas est rapporté en détail.

Cette voie est démontrable dans les radiogrammes thoraciques de profil; ceux-ci devraient être effectués dans tous les cas d'emphysème médiastinal de cette nature.

Les études anatomique démontrent, de même que les tentatives d'investigation paraissent le confirmer, l'importance de la couche fibro-musculaire formée par la continuité du transverse et du diaphragme. L'injection d'air à la surface de cette couche représente un plan tissulaire apte à laisser passer l'air au-dessus du diaphragme et, de la, dans le médiastin.

Les auteurs indiquent qu'il y a lieu de choisir la gaine du grand droit de l'abdomen comme siège de la ponction car, en raison de sa fusion avec la couche postérieure du muscle oblique interne, l'aponévrose du transverse ne présente pas d'espace libre à sa surface.

Addendum

Since completion of this study, the writers have encountered another patient with mediastinal emphysema following a pneumoperitoneum refill of 1,000 cc. of air administered at the local Veterans Administration Regional Office. During and immediately after this procedure, he experienced epigastric and low retrosternal distress which gradually ascended into the neck during the remainder of the day. That night, eight hours after receiving air, he came to the hospital complaining of pain in both jaws when chewing and moderately severe dysphagia. Physical examination disclosed subcutaneous emphysema of the neck, barely palpable emphysema of the deep anterior abdominal wall, and the presence of Hamman's sign. A postero-anterior roentgenogram of the chest presented an extremely well-defined radiolucent zone between each cardiac border and the mediastinal pleurae. A lateral view disclosed the presence of air in the anterior abdominal wall extending in linear fashion upward into the mediastinum.

Thus, of four patients with this complication, all three who had lateral roentgenograms showed the presence of air following the same route from the anterior abdominal wall into the mediastinum. The other patient, the first one seen by the writers, presented unmistakable clinical and roentgenographic evidence of mediastinal emphysema, but, unfortunately, a lateral roentgenogram was not obtained.

REFERENCES

(1) Hamman, L.: Remarks on diagnosis of coronary occlusion, Ann. Int. Med., 1934, *8*, 417.
(2) Hamman, L.: Spontaneous interstitial emphysema of the lungs, Tr. A. Am. Physicians, 1937, *52*, 311.
(3) Hamman, L.: Note on mechanism of spontaneous pneumothorax, Ann. Int. Med., 1939, *13*, 923.
(4) Hamman, L.: Spontaneous mediastinal emphysema, Bull. Johns Hopkins Hosp., 1939, *64*, 1.
(5) Hamman, L.: Mediastinal emphysema (The Frank Billings Lecture), J.A.M.A., 1945, *128*, 1.
(6) Macklin, C. C.: Pneumothorax with massive collapse from experimental local overinflation of lung substance, Canad. M.A.J., 1937, *36*, 414.
(7) Macklin, C. C.: Transport of air along sheaths of pulmonic blood vessels from alveoli to mediastinum: Clinical complications, Arch. Int. Med., 1939, *64*, 913.

(8) Macklin, C. C., and Macklin, M. T.: Pulmonic interstitial emphysema and its sequelae: Anatomical interpretation, Essays in Biology, H. Evans Birthday Volume, 1943, Univ. Calif. Press, Berkeley, Calif., p. 337.

(9) Macklin, M. T., and Macklin, C. C.: Malignant interstitial emphysema of the lungs and mediastinum as an important occult complication in many respiratory diseases and other conditions: An interpretation of the clinical literature in the light of laboratory experiment, Medicine, 1944, *23*, 281.

(10) Towbin, M. N.: Mediastinal emphysema occurring with therapeutic pneumoperitoneum: Report of ten cases, Ann. Int. Med., 1951, *35*, 555.

(11) Jehn, W., and Nissen, R.: Pathologie und Klinik des Mediastinal-emphysems, Deutsche Ztschr. f. Chir., 1927, *206*, 221.

(12) Banyai, A. L., and Jurgens, G. H.: Mediastinal emphysema as a complication of artificial pneumoperitoneum, J. Thoracic Surg., 1939, *8*, 329.

(13) Clifford-Jones, E., and MacDonald, N.: Pneumoperitoneum in collapse therapy of pulmonary tuberculosis, Tubercle, 1943, *24*, 97.

(14) Anderson, N. L., and Winn, W. D.: Pneumoperitoneum and diaphragmatic paralysis, Am. Rev. Tuberc., 1945, *52*, 380.

(15) Aslett, E., and Jarman, T. F.: Reaction after pneumoperitoneum treatment, Lancet, 1945, *1*, 304.

(16) Simmonds, F. A. H.: Air embolism and pneumomediastinum in artificial pneumoperitoneum, Lancet, 1946, *1*, 530.

(17) Moyer, R. E.: Pneumoperitoneum and phreniclasia, Dis. of Chest, 1949, *15*, 43.

(18) Lemanissier, A. F., Breant, J., and Fourchon, J.: L'emphyseme mediastinal complication du pneumoperitoine (a propos de deux observations), Poumon, 1950, *6*, 543.

(19) Weiss, W., and Stanley, C. O.: Mediastinal emphysema due to therapeutic pneumoperitoneum, J. Phila. Gen. Hosp., 1951, *2*, 13.

(20) Small, M. J., and Fremont, R. E.: Mediastinal emphysema complicating induction of pneumoperitoneum, Am. Rev. Tuberc., 1951, *63*, 591.

(21) Schwaderer, A.: Zur Frage des Mediastinalemphysems als Komplikation beim künstlichen Pneumoperitoneum; Versuch einer Erklärung der Entstehung an Hand von drei Fällen, Tuberkuloseartz, 1951, *5*, 599.

(22) Morrison, J. B.: Pneumomediastinum complicating artificial pneumoperitoneum, Brit. J. Tuberc., 1949, *43*, 18.

(23) Rives, J. D., and Baker, D. D.: Anatomy of the attachments of the diaphragm: Their relation to the problems of the surgery of diaphragmatic hernia, Ann. Surg., 1942, *115*, 745.

Editorial

The Problem of Tuberculosis in Psychotics

Case finding of active tuberculosis is at such a high level of efficiency in this country that we are open to question when, with all our efforts to find and treat the victims of this disease, we allow a dangerous focus of tuberculosis infection to go inadequately explored and reluctantly treated.

This focus comprises the unfortunate and all-too-often forgotten patients who are hospitalized in our institutions for the mentally ill. The danger of exposure of psychotic patients to tubercle bacilli is a phenomenon emphatic enough in itself to need no words to play it up, but its importance to society is likely to be but dimly realized. Its danger, therefore, is as great as its recognition is small. We are near to absurdity when we make great effort to find tuberculosis in our general population and ignore it in our psychotics. The number of tuberculous patients varies with different institutions, but, on the whole, it is much higher than in the general population. The reason for this increased incidence is obscure. Various theories are offered: that the psychotic undergoes some kind of metabolic change in which his resistance falls to such a degree that he becomes an easy victim of the disease; that the psychosis causes a person to eat poorly, to become dilapidated, and to be careless of himself; or that he is in intimate contact with unknown and undiscovered cases of active tuberculosis. Probably all factors are active. Whatever the reason, it seems that the incidence of tuberculosis is greatest in those patients who have been hospitalized for five years or more. We might possibly gain some valuable information by making an energetic effort to find all infected patients and to treat them with every facility we have at hand. If we could reduce the incidence of the disease in this way, we would have at least part of an answer.

When the psychotic is identified and placed in an institution, he is too often dismissed from mind. The psychotic himself has withdrawn from the world of reality and from acceptable human activity. He cannot or will not make known the discomfort resulting from his disease. But the phthisiologist may not withdraw from the vexatious reality presented by the tuberculous psychotic himself. There is no place for an attitude of hopelessness in the treatment of mental illness. Psychotics can and frequently do recover; and, having recovered, they are at a grievous disadvantage if they must be kept hospitalized for an additional period for the tuberculosis which they acquired while under treatment for the psychoses.

There is a simple solution to the "special" problems involved in the diagnosis and treatment of tuberculosis among the psychotic. That is, never to allow the psychosis to interfere with the application of diagnostic methods and treatment procedures. The psychosis is a very inconvenient and distressing complication of the tuberculosis, but it is not the primary condition; it is the factor which makes diagnosis and treatment of the tuberculosis more urgently necessary.

Every form of diagnostic procedure should be carried out with psychotic patients. Whether it is sputum collection, extraction of gastric contents, roentgenograms of the chest, planigrams, fluoroscopy, or bronchoscopy, it can be done. If the patient's behavior is such as to defeat any necessary procedure, the situation becomes more serious and evaluation of the tuberculous condition becomes correspondingly more important. Free use of sedation may be employed successfully with any diagnostic procedure. Whatever the situation may be, the patient must never be allowed to order his own regimen by defeating the efforts of his physician.

We have no statistics to offer regarding the difference in infectiousness between the psychotic tuberculous patients and the nonpsychotic. The impression, however, is that the former are more infectious because many are dilapidated; they are discovered with greater difficulty; and are apt to carry about their disease for indefinite periods before it is discovered. Tuberculosis can make great advances between yearly roentgenograms.

Our impression of the course of tuberculosis in the mentally ill cannot as yet be reinforced by statistical data. There are too many unknown factors and uncontrolled variables. However, there has been an impression—and it is only an impression—that tuberculosis in the mentally ill is more indolent, less responsive to treatment, and, if once made inactive, more prone to relapse. Whether we could say the same if tuberculous psychotics could be treated under ideal conditions, we cannot be certain; but our results indicate that the course of tuberculosis in the mentally ill will change for the better in proportion to the care and attention given to prevention and treatment.

The history of illness given by a psychotic may be surprisingly accurate, or it may be misleading, irrelevant, and absurd; or there may be no history at all because the patient is mute. Diagnosis must often depend on factors other than the history. The physician must maintain a high "index of suspicion" for the disease, and all personnel must be thoroughly indoctrinated to be on the lookout for changes of attitude and behavior in patients who have no other way of showing they have become ill. If the physician is alert to the valuable information brought to him by nurses, aides, and others who come in contact with patients, he will be quick to order the roentgenogram which may show the early involvement. Diagnostic methods should then be followed as closely as with nonpsychotics. Sputum should be persistently collected and examined. Roentgenograms should be made regularly. The patient may not be cooperative when the roentgenogram is taken; but, with enough persuasion, gentle handling, and proper sedation, the desired film can be obtained. It has been our experience at the Veterans Administration Hospital at Lyons that, if the patient is observed for a time when he is quiet, the roentgenogram of the chest can be obtained without difficulty. These patients vary in their mood, and there are frequent intervals when they are cooperative.

Refusal to eat is a frequent occurrence among psychotics. The loss of weight which results from this should warn the physician of its potentialities and of the problem of differential diagnosis involved.

The problems presented in the treatment of tuberculous psychotics resemble

those of diagnosis, but the difficulties are greater because more must be done. Our attitude is that the patterns of treatment for the psychotic must be the same as those for the nonpsychotic.

Rest is still the basis of treatment. Great care is taken to teach all patients the rest regimen, for it is possible to teach psychotics a great deal. But it is easy to take for granted that all psychotics can be taught equally well to follow a rigid regimen. However, many patients require longer and more persistent training, and among these will be a certain minimum who will break treatment no matter how carefully taught and how closely watched. One may reasonably ask how large this irreducible minimum should be, but there can be no answer. The number will vary to a degree with the type of patient; but it will vary more with the tolerance of the personnel in charge. An energetic, well-trained, and careful group will have only a small number; and a good portion of the time it will be possible to have the exceptional patients follow the regimen quite well. Where there is tolerance to breaks in treatment, the number of uncooperative patients will increase accordingly.

It is reasonable to speculate what may be done with a patient who is overactive, resistive, assaultive, and not amenable to persuasion, but who has far advanced tuberculosis with a sputum rich in tubercle bacilli. Treatment then becomes a joint matter between the phthisiologist and the psychiatrist. Shock therapy and lobotomy may be in order and, if so, can be carried out as with the nontuberculous psychotics. These are instances of the predominance of the psychosis as the disease of greatest urgency, but, when the patient becomes more amenable to the hospital regimen, tuberculosis once again becomes the more important problem. It is obvious and freely admitted that we are involved with a group of patients who require much more care and attention than either the nonpsychotic tuberculous or the nontuberculous psychotic, but this is to be expected when there is a combination of two very important conditions. These patients require more care and attention, not less.

Where the indications are good, a combination of surgical procedures with antimicrobial therapy is the method of choice because it offers the quickest results. Thoracoplasty, lobectomy, segmental and wedge resections are carried out exactly as with nonpsychotics.

In addition to the benefits of the rest regimen and the free use of surgical procedures, a great deal may be expected from extensive employment of streptomycin with para-aminosalicylic acid or with isoniazid. Minimal and moderately advanced cases show a surprising response with remarkable clinical and roentgenographic improvement, and the more advanced cases may be improved to a degree where previously contraindicated surgical procedures become possible. Patient cooperation can be a problem in antimicrobial therapy. Ordinarily, para-aminosalicylic acid or isoniazid by mouth and the injection of streptomycin are accepted by psychotics with as little resistance as by nonpsychotics, but there will be some who will accept the injections and not the oral medication, and there will be others who will take the oral medication but will resist the injection. Sometimes much persuasion is necessary, and occasionally a patient must be

held while he receives his injection, and the oral medication must be given in soluble form mixed with food. With a stable group of patients who may not break treatment by leaving the hospital at will, it is possible to apply all methods of treatment as they are indicated. We need not accept unchallenged that psychotics must somehow be more subject to tuberculosis than nonpsychotics.

Originally, our efforts began with systematic case finding and the establishment of a system of continuous re-examination of our tuberculous patients, both active and inactive, and regular follow-up of all personnel. Patients were systematically trained to follow the rest regimen; and pneumothorax, pneumoperitoneum, and thoracoplasty were employed whenever indicated. Streptomycin alone was used infrequently in order to avoid the appearance of resistant cases. With the advent of para-aminosalicylic acid and isoniazid, an all-out regimen of streptomycin combined with these agents was established with gratifying results. The appearance of new cases has diminished almost to a vanishing point. Sputum and gastric content examinations positive for tubercle bacilli have been very infrequent. We have no patients who are receiving pneumothorax or pneumoperitoneum and none in whom thoracoplasty is indicated. Segmental and wedge resection are employed occasionally. We have learned that with vigorous application of all methods of therapy the whole patient, with his tuberculosis and psychosis, can be treated successfully and that tuberculosis in a neuropsychiatric institution can be controlled.

Abraham M. Balter
Michael Pilpel
Lyons, New Jersey
Harold S. Hatch
Morristown, New Jersey
George N. J. Sommer, Jr.
Trenton, New Jersey

Notes

RESULTS WITH OXIDATION-REDUCTION DYES IN THE DETERMINATION OF VIRULENCE OF MYCOBACTERIA

The four indophenol dyes recommended by Wilson, Kalish, and Fish (Am. Rev. Tubere.: 1952, *65*, 187) were tested with 11 strains of tubercle bacilli, 44 acid-fast saprophytes, and BCG. The tests were performed in 11 mm. by 75 mm. tubes as described by Wrinkle and Patnode (Am. Rev. Tubere.: 1952, *66*, 99) since it was believed that spot plates were too dangerous when used with cultures of tubercle bacilli.

Stock solutions of the dyes were prepared in phosphate buffer solution of pH 7.0 (5.99 gm. NaH_2PO_4, 7.098 gm. Na_2HPO_4, diluted to 1 liter with distilled water) as follows: 5 mg. of the first dye, phenol indophenol, in 10 ml. buffer solution; 5 mg. of the second dye, sodium benzenoneindophenol, in 5 ml. of buffer solution; 5 mg. of the third dye, sodium benzenoneindo-3′-chlorophenol, in 25 ml. of buffer solution; and 5 mg. of the fourth dye, sodium 2,6-dibromobenzenone-indophenol, in 25 ml. of buffer solution. Dyes Nos. 2 and 3 were dissolved with the aid of heat, but all of dye No. 3 did not dissolve. It was filtered to remove the undissolved portion. The stock solutions were stored in screw-cap jars at refrigerator temperature.

On the day the tests were made, dilutions of the stock solutions were made as follows:

Dye No. 1, phenol indophenol, 1 ml. added to 5 ml. of buffer solution

Dye No. 2, sodium benzenoneindophenol, 1 ml. added to 3 ml. of buffer solution

Dye No. 3, sodium benzenoneindo-3′-chlorophenol, 3 ml. added to 2 ml. of buffer solution

Dye No. 4, sodium 2,6-dibromobenzenone-indophenol, 1 ml. added to 7.5 ml. of buffer solution

No. 1 was pink; *No. 2*, deep wine; *No. 3*, pale orange; and *No. 4*, blue.

A preliminary test was performed using a pool of the four dyes, 0.15 ml. of each. This pool was purple-red in color. A loopful of culture, approximately 5 to 10 mg., was added to each and shaken; the tubes were examined after fifteen minutes, thirty minutes, forty-five minutes, and one hour. Results were based on the fifteen-minute and thirty-minute readings. If the results were clear-cut, i.e., either complete decolorization of the dye (indicating nonvirulent strains) or no change (indicating virulent strains), no further tests were done; but if a delayed or partial reaction was obtained, the tests were repeated using the single dyes in 0.3 ml. amounts. A tube of uninoculated dye, a tube with a strain known to react, and a tube with a strain which did not decolorize the dyes were included as controls with each set of tests.

Fifty-six strains, with which guinea pigs had been inoculated, were tested with these dyes. Thirteen strains were acid-fast branched forms; 11 of these decolorized the dyes, one failed to decolorize, and one partially decolorized both the pool and the single dyes. One of the strains which decolorized required forty-five minutes for the change; and two, thirty minutes; while the others reacted at fifteen minutes. Guinea pigs inoculated intraperitoneally with these branched strains showed lesions of the liver and enlarged mesenteric nodes but no lesions of the spleen or other lymph nodes.

Thirty strains of acid-fast bacilli which produced only local lesions or none in guinea pigs were tested. Thirteen failed to decolorize, 12 partially decolorized, and only 5 completely decolorized the dye in thirty minutes. These strains included a stock culture of *Mycobacterium smegmatis* which partially decolorized, and one of *Mycobacterium phlei*

which failed to decolorize. BCG also gave the reaction of a virulent strain and a strain of avian tubercle bacilli pathogenic for chickens gave a partial reaction. Eleven strains known to produce tuberculous lesions in guinea pigs were also tested. An old stock strain of human tubercle bacilli which had not recently been tested in animals and one of 2 bovine strains partially decolorized, but the other 9 failed to do so.

In addition to these strains, 88 strains of acid-fast bacilli which either did not resemble tubercle bacilli or grew at room temperature were tested. Guinea pigs were not inoculated with these cultures. Thirty-eight strains decolorized the dyes, 19 caused partial decolorization, and 31 failed to decolorize.

The test seems to give fairly reliable results with human tubercle bacilli pathogenic for guinea pigs since the only one which failed to react was an old stock strain which had not been tested in animals for some time. The results with acid-fast saprophytes were very irregular, however, since approximately 35 per cent failed to decolorize either the pool or the single dyes. The results with the acid-fast branched forms were more consistent but were not completely uniform. Thus, the test could be used in connection with others but should not be relied on as the sole criterion for pathogenicity.

Division of Laboratories and Research
New York State Department of Health
Albany, New York

Mary E. Clark
Elizabeth S. Forrest

April 8, 1953

A NEW MULTIPURPOSE MAGNIFYING X-RAY VIEWER[1]

A new magnifying roentgenogram viewer has been designed to satisfy the need in a tuberculosis control clinic for viewing photoroentgen and conventional roentgenograms under magnification with one device.

The magnifying viewer (figure 1) consists essentially of a 14- by 17-inch X-ray view box, encased in a plywood frame. The lens (9-inch diameter; 18-inch focal length) is mounted on two tracks, providing motion across the width and length of the viewer.

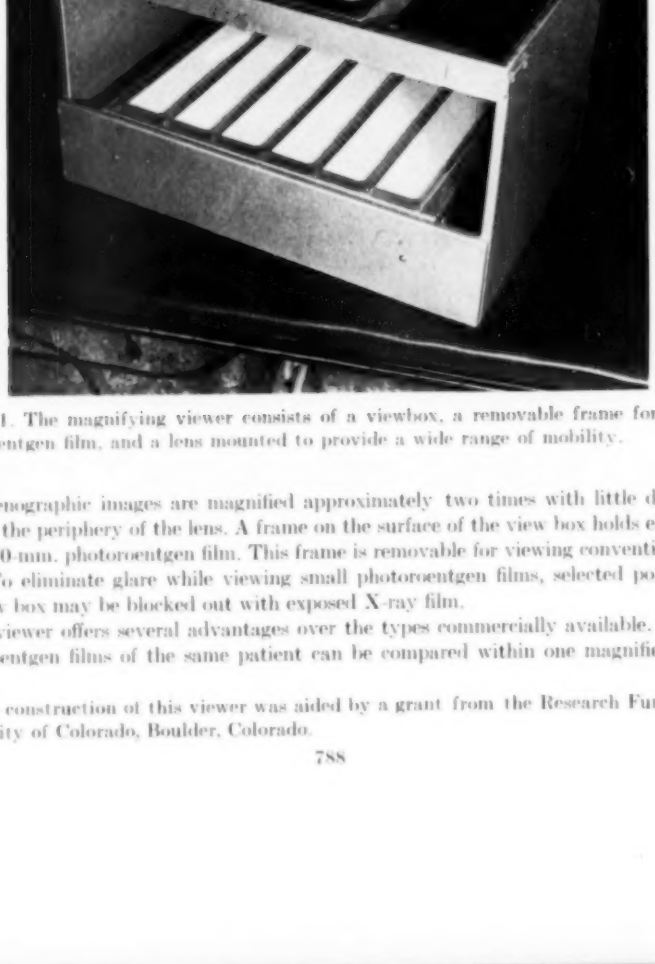


FIG. 1. The magnifying viewer consists of a viewbox, a removable frame for holding photoroentgen film, and a lens mounted to provide a wide range of mobility.

Roentgenographic images are magnified approximately two times with little distortion even at the periphery of the lens. A frame on the surface of the view box holds either cut or roll 70-mm. photoroentgen film. This frame is removable for viewing conventional size films. To eliminate glare while viewing small photoroentgen films, selected portions of the view box may be blocked out with exposed X-ray film.

The viewer offers several advantages over the types commercially available. Interval photoroentgen films of the same patient can be compared within one magnified visual

[1] The construction of this viewer was aided by a grant from the Research Fund of the University of Colorado, Boulder, Colorado.

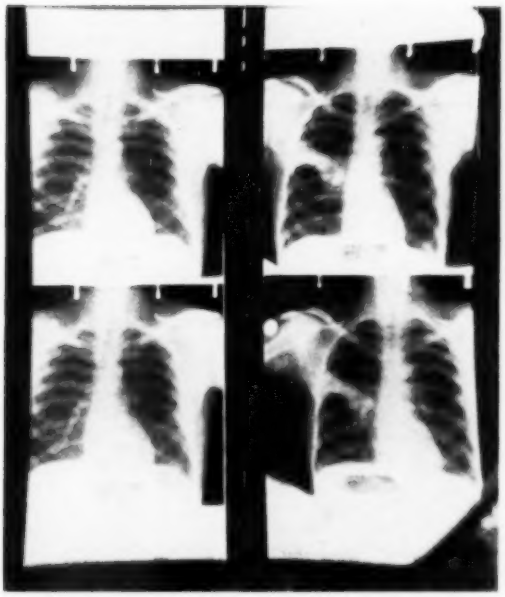


FIG. 2. A unique feature is the visualization of four 70-mm. photoroentgen films in one field for comparison.

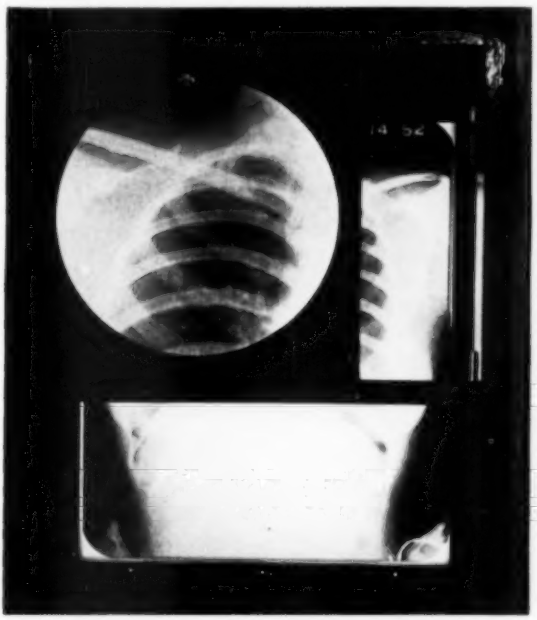


FIG. 3. Conventional roentgenograms can be magnified on the same viewer.

field (figure 2). Several observers can view the magnified image simultaneously, an important feature in teaching programs. Conventional roentgenograms are magnified by simply removing the photoroentgen film frame from the surface of the view box (figure 3).

EMANUEL SALZMAN

DIVISION OF RADIOLOGY
DENVER GENERAL HOSPITAL
DENVER, COLORADO

May 25, 1953

FAILURE OF PARA-ISOBUTOXYBENZALDEHYDE THIOSEMICARBAZONE AS AN ANTITUBERCULOUS DRUG IN MAN

An investigation of the feasibility of the use of *p*-isobutoxybenzaldehyde thiosemicarbazone[1] in tuberculosis in humans was undertaken at the New York Hospital-Cornell Medical Center in August, 1951. The potentialities of this drug, as indicated by *in vitro* studies and animal investigation conducted at the Squibb Institute, suggested that it has an activity approximately three times greater and a toxicity one-half that of 4-acetylaminobenzaldehyde thiosemicarbazone (amithiozone).

As an initial step, the concentrations of the thiosemicarbazone in the blood and urine of the patients were determined by the method of Burke and Titus of the Squibb Institute. The method involved extraction of the drug into an n-hexanol phase by shaking. After separating the phases, the drug could be quantitated from the n-hexanol phase by its absorption at 330 mu, as measured by a Beckman quartz spectrophotometer according to Beer's Law. The method was sensitive to 0.5 γ per ml. and was reproducible within 3 to 5 per cent.

No measurable blood concentrations were obtained with a single 50 mg. oral dose to 2 patients. On continued drug administration of 50 mg. orally per day, however, 1.1 to 1.3 γ of drug per ml. of blood appeared in the blood of both patients on the third day of drug administration. The maximum blood concentrations obtained with a total daily dose of 300 mg. (divided into three doses) were between 2.2 and 2.7 γ of drug per ml. Subsequently, although the dose was increased to a total daily dose of 350 and 400 mg., the concentration in the blood still ranged only between 1.0 and 3.0 γ per ml. of blood. The urinary excretions of drug by the same 2 patients who received continuous daily drug therapy varied between 5 and 15 per cent of the total daily dose.

Continuous therapy with the thiosemicarbazone for a period of approximately six months was initiated in 2 patients with chronic pulmonary tuberculosis on September 19, 1951. The total daily dose administered orally at twenty-four–hour intervals was 50 mg. for the first two weeks and 100 mg. for the succeeding week. Thereafter, the dose was gradually increased to 350 mg. daily, which was maintained for two and one-half months and then increased to 700 mg. daily for an additional month. During the last month of therapy, the total daily dose was lowered to 200 mg. of drug.

The following laboratory examinations for signs of toxicity were performed at frequent intervals: electrocardiogram, complete blood count, hematocrit, urinalysis, urea clearance test, bromsulfalein test, determinations of blood urea nitrogen, serum protein, albumin-globulin ratio, alkaline phosphatase, serum bilirubin, and thymol turbidity.

The only finding suggestive of potentially serious toxicity was a persistent leukopenia in one of the 2 patients. This appeared after four weeks of therapy and was of mild degree. The total leukocyte count during the forty-two weeks of therapy ranged from 3,200 per cu. mm. to normal values, but was usually, after the first month, between 4,000 and 6,000 cells per cu. mm. The granulocytes never fell below 40 per cent (in a total count of 3,800) and were usually between 40 and 60 per cent, with a low proportion of immature forms (0 to 4 per cent). Both patients exhibited occasional faint traces of albumin and rare casts in the urine.

Appropriate observations for evidence of therapeutic effect were made at frequent intervals. One patient (J. E.), whose disease was moderately advanced, showed slight to

[1] The *p*-isobutoxybenzaldehyde thiosemicarbazone was synthesized by and supplied through the courtesy of E. R. Squibb & Sons.

moderate regression of pulmonary infiltration and shrinkage of cavity up to the sixth month of therapy, when roentgenographic deterioration occurred as evidenced by enlargement of the cavity. Therapy was discontinued for this reason after twenty-six weeks. The sputum had remained positive for tubercle bacilli on smear and culture. The other patient (R. S.), whose disease was far advanced with little reversible component and old fibrotic cavities, showed neither roentgenographic improvement nor deterioration during forty-two weeks of therapy, in the last five of which he also received isoniazid. This patient's sputum became negative for *M. tuberculosis* on culture during the last five weeks of administration of the thiosemicarbazone. Therapy was discontinued because of severe toxic manifestations which occurred in other patients treated for a shorter period, as is described below.

After the initial trials of six months or more of continuous therapy with the thiosemicarbazone in 2 patients, as described, 8 more patients with chronic pulmonary tuberculosis received the drug for periods ranging from three to thirteen weeks. Two of these patients developed neutropenia progressing to agranulocytosis. One had a gradually progressive neutropenia which started in the third week of therapy, with a decline in the total leukocyte count to 2,500 per cu. mm. by the end of the fourth week. A further decline to 1,800 leukocytes per cu. mm. occurred in the next four days, and the neutrophils declined from 36 to 1 per cent in the same period despite discontinuance of thiosemicarbazone therapy. The other patient experienced a sudden drop from a normal leukocyte count at the end of the fourth week to a total count of only 1,500 per cu. mm. four days later. This fall was accompanied by a complete disappearance of granulocytes from the peripheral blood smears. Both patients recovered after administration of the thiosemicarbazone was stopped. Both patients received penicillin, and the second patient also received dihydrostreptomycin and corticotropin for treatment of the agranulocytosis.

With the occurrence of agranulocytosis in the second patient, further administration of the thiosemicarbazone was discontinued in all patients. Prior to discontinuance of the drug, neutropenia of slight to moderate degree was noted in 2 others, including the patient previously mentioned who had received the drug for forty-two weeks. One patient developed anemia of moderately severe degree (hemoglobin concentration of 9.0 gm.; erythrocytes, 2.1 million per cu. mm.; hematocrit, 24) in a five-week period of therapy. The hematologic abnormalities returned to normal after cessation of therapy and have remained normal since then without further treatment. Other toxic manifestations of the thiosemicarbazone were of minor degree and consisted of slight albuminuria, 8 cases; eosinophilia, 6 to 14 per cent in 4 cases; an abnormal cephalin flocculation, one case; and mild glycosuria, one case.

One patient (E. J.) died after seven days of therapy with extensive bilateral fibrocaseous tuberculosis and aspiration pneumonia, associated with terminal acute gastric dilatation. The death was not attributed to any toxic effect of the drug. Another patient (R. S.) died four months after discontinuance of therapy with the thiosemicarbazone, apparently of cardiac arrest three days after a pulmonary resection. This death also appears to be in no way attributable to the medication. Post-mortem examinations were performed in both cases.

The 8 surviving patients have exhibited no evidence of delayed toxic manifestations. All have received isoniazid subsequently. This therapy was instituted before discontinuance of the thiosemicarbazone, and the two drugs were administered concurrently for one to six weeks. One of the patients who developed agranulocytosis while receiving the thiosemicarbazone was also receiving isoniazid. The isoniazid was discontinued at the time of the cessation of the thiosemicarbazone, and the former drug was omitted for ten days

until the hematologic abnormalities disappeared. There was no recurrence of agranulocytosis or neutropenia after resumption of isoniazid therapy in this patient.

No conclusions are possible concerning the antituberculous activity of the thiosemicarbazone preparation which was used. Several patients who received isoniazid and the thiosemicarbazone concurrently improved appreciably in the relatively brief period of combined therapy, but whether any of the improvement is attributable to the thiosemicarbazone is indeterminable.

Evidence of the emergence of tubercle bacilli resistant to the thiosemicarbazone was obtained from studies *in vitro* of cultures obtained late in the course of treatment of one of the 2 patients treated for six months. The precise degree of drug resistance was uncertain because of technical difficulties with the method for testing drug susceptibility.

In summary: The drug *p*-isobutoxylbenzaldehyde thiosemicarbazone was administered in therapeutic trials to 10 patients with pulmonary tuberculosis. Four patients developed neutropenia which progressed to agranulocytosis in 2 instances. One patient developed a severe toxic anemia. Recovery from the toxic manifestations occurred promptly on discontinuance of the drug. Nevertheless, the toxic reactions were of such character and severity as to preclude any further clinical investigation of this drug in the treatment of tuberculosis.

Department of Medicine
New York Hospital-Cornell Medical Center, New York 21, New York

Carl Muschenheim
DuMont F. Elmendorf, Jr.
William D. Cawthon
Walsh McDermott

March 1, 1953

PARA-ISOBUTOXYBENZALDEHYDE THIOSEMICARBAZONE IN THE TREATMENT OF PULMONARY TUBERCULOSIS

Thiosemicarbazones have a definite inhibitory effect on the growth of tubercle bacilli. The clinical usefulness of this group of compounds is limited, however, by their toxic effects, particularly on the liver and the bone marrow. Amithiozone (*p*-acetylaminobenzaldehyde thiosemicarbazone) has been used extensively in Europe and to a limited degree in North America. It is only moderately effective in dosages which can be employed clinically, but it has given enough promise to encourage the study of other thiosemicarbazones.

p-Isobutoxybenzaldehyde thiosemicarbazone[1] has an *in vitro* inhibiting effect four times that of amithiozone and is slightly less soluble than amithiozone. The manufacturers of the drug report that its chronic toxicity in the dog was less than that of amithiozone and that its antituberculous activity in the mouse test was three times that of amithiozone

TABLE 1

BLOOD CHEMISTRIES

PATIENT	WEEK OF THERAPY	SODIUM mE/L	POTASSIUM mE/L	CHLORIDE mM/L	CARBON DIOXIDE mM/L	SERUM pH	CALCIUM Mg PER 100 ML.	PHOSPHORUS Mg PER 100 ML.	T.P.* Gm. PER 100 ML.	ALBUMIN, Gm. PER 100 ML.	GLOBULIN, Gm. PER 100 ML.	GLUCOSE TOLERANCE TEST
1	0								7.42	4.51	2.91	
	4								7.63	4.42	3.21	
	8								7.18	4.33	2.85	
2	0	138	4.1	96.2	31.5	7.40	9.7	3.6	6.90	4.06	2.84	March 7, 1952, normal. Trace of reduction in urine at 157 mg. per 100 ml. of blood glucose
	6	130	4.3	96.8	34.3	7.50			7.03	3.99	3.04	
	8	139	5.5	92.0	34.9	7.43						
	15								7.30	4.57	2.73	
3	0	138	4.1	100.8	29	7.39	9.6	4.4	6.96	5.01	1.95	April 18, 1952, normal
	3	141	4.5	100.4	31.5	7.49						
	13	135	4.1	101	31	7.36	10.1	4.8	6.44	5.07	1.37	
4	0								7.82	4.50	3.32	
	3								8.00	4.75	3.25	
	8								7.94	4.60	3.34	

* Total plasma proteins.

The primary purpose of this study was to determine the toxicity of the *p*-isobutoxybenzaldehyde derivative rather than to evaluate its therapeutic value. Four patients with active pulmonary tuberculosis were treated for periods ranging from sixty-three to ninety-three days, with a minimum daily dose of 200 mg. and a maximum daily dose of 500 mg.

All four patients remained afebrile and all gained weight during the time they received the thiosemicarbazone. No serious toxic effects were observed in any patient, even at the maximum dosage of 500 mg. daily. Patients 1, 2, and 4 had a slight drop in hemoglobin concentration, and Patient 1 showed a depressed leukocyte count with a reduction in the

[1] The *p*-isobutoxybenzaldehyde thiosemicarbazone was synthesized by and supplied through the courtesy of E. R. Squibb & Sons.

percentage of polymorphonuclear cells. No significant alterations occurred in the values for various chemical tests of the blood (table 1) or in the renal and hepatic function tests.

The therapeutic effects of the drug were of interest. Patient 1 had long-standing chronic fibrotic disease in which little roentgenographic change could be expected with any drug. Her sputum remained consistently positive for acid-fast bacilli on direct smear and there was only a slight reduction in daily sputum volume. Patient 2 had sputum abundant in acid-fast bacilli on admission to the hospital, and sputum became negative on treatment with streptomycin and para-aminosalicylic acid (PAS). When therapy was changed to the thiosemicarbazone, the sputum again became positive for acid-fast bacilli. After completing the thiosemicarbazone studies, this patient was placed on streptomycin and isoniazid, and the sputum became "negative" on direct smear almost immediately. The roentgenographic appearance of this patient's disease during the thiosemicarbazone therapy showed approximately the same degree of improvement as was shown during his treatment on the other two regimens. Patient 3 exhibited moderate roentgenographic improvement and his sputum "converted" from Gaffky IV to "negative" on direct smear during the treatment with the thiosemicarbazone. Patient 4 showed moderate improvement as judged by the roentgenograms, but her sputum remained positive for acid-fast bacilli on direct smear.

In summary: In so far as the present limited study is concerned, *p*-isobutoxybenzaldehyde thiosemicarbazone exhibited relatively little toxic effect in doses as high as 400 to 500 mg. daily. However, this compound did not show a pronounced therapeutic effect. As other cooperating investigators have observed agranulocytosis with its use, it is unlikely, therefore, that *p*-isobutoxybenzaldehyde thiosemicarbazone will find an established place in the treatment of tuberculosis.

Department of Medicine
University of Chicago
Chicago 37, Illinois

William R. Barclay
Gwendolyn L. Morris
R. H. Ebert

October 1, 1952

PARA-ISOBUTOXYBENZALDEHYDE THIOSEMICARBAZONE IN PULMONARY TUBERCULOSIS

An investigation of the possible therapeutic value of *p*-isobutoxybenzaldehyde thiosemicarbazone[1] was initiated in the Veterans Administration Hospital, Montrose, New York, in April, 1952. The study was integrated with a parallel study at The New York Hospital-Cornell Medical Center (Muschenheim *et al.*, p. 791) after initial trials of the drug in 2 patients treated there for six months or longer indicated the feasibility of more extended trials.

A total of 7 patients received the thiosemicarbazone in a dosage of 300 mg. per day during the first two weeks, and 400 mg. per day thereafter. The daily dose was given orally in equally divided amounts at 9 a.m. and 9 p.m. One patient was treated for four weeks; one, for five weeks; the remaining 5 patients were treated for nine weeks. All of the patients had moderately or far advanced pulmonary tuberculosis of long standing, associated with mental illness. All had previously received streptomycin and para-aminosalicylic acid (PAS), and 5 had infections with tubercle bacilli of demonstrated resistance to one or both of these drugs.

The patient whose treatment was discontinued at four weeks had a rising blood urea nitrogen. Therapy was terminated because of this and the patient's evidently hopeless condition, which had been so even before the start of treatment. He had advanced amyloidosis, as indicated by 100 per cent Congo red adsorption and an elevation of the blood urea nitrogen. During thiosemicarbazone therapy, the blood urea nitrogen rose from 25 to 66 mg. per 100 ml., at which point drug treatment was stopped. The patient died one week later, the blood urea nitrogen having risen to 123 mg. per 100 ml. on the day before death. Post-mortem examination confirmed the diagnosis of extensive amyloidosis, which was considered to be the immediate cause of death. Certain histologic changes in the lungs, where there was extensive tuberculosis, suggested a recent healing tendency, but it was not possible to relate this to the thiosemicarbazone therapy.

The patient whose treatment was discontinued at five weeks was a severely disturbed patient mentally, and the therapy was terminated because of his refusal to cooperate. There had been no toxic symptoms attributable to the drug, but there was evidence of anemia with decline of the hemoglobin, erythrocyte count, and hematocrit from normal pretreatment values to 10.7 gm., 4.1 million cells per cu. mm., and 31 per cent, respectively. The blood count returned to normal after discontinuance of the thiosemicarbazone therapy.

Treatment was discontinued at the end of nine weeks in the remaining 5 patients because of the development of anemia in 3 of them and because of reports of neutropenia and agranulocytosis in patients treated elsewhere, although this complication was not encountered in any of the patients in the present series.

Significant anemia occurred in 4 patients who had normal hemograms before therapy. In one patient there was a sharp fall of the hemoglobin in the first week from 13.7 gm. to 10.4 gm. per 100 ml., and a corresponding decline in the erythrocyte count from 4.7 million to 3.7 million per cu. mm. There followed a gradual return to normal by the ninth week, before the discontinuance of thiosemicarbazone therapy. In the other 3 patients the development of anemia was more gradual, the hemoglobins and erythrocyte counts reaching equivalent low levels only by the eighth or ninth week. As the therapy was then

[1] The *p*-isobutoxybenzaldehyde thiosemicarbazone was synthesized by and supplied through the courtesy of E. R. Squibb & Sons.

discontinued, it is not known whether recovery would have taken place under continued administration of the drug. One patient reached a low of 8.0 gm. of hemoglobin per 100 ml. and 2.3 million erythrocytes per cu. mm. at the eighth week and, with partial recovery, to 8.9 gm. and 3.3 million erythrocytes at the end of the ninth week. The hemograms of all of the patients returned to normal after the administration of thiosemicarbazone was discontinued.

The blood urea nitrogen increased progressively only in the one patient who had extensive amyloid disease. It is thought that the renal failure in this case was caused by the disease and that it was primarily unrelated to the drug, although this may have contributed to its progression. In another patient, whose blood urea was slightly elevated to 23 mg. per 100 ml. initially, the value rose further during therapy to 40 but declined to 28 mg. per 100 ml. before the end of treatment. A third patient, whose blood urea nitrogen was normal initially, had a transient elevation to 24 mg. per 100 ml. during therapy. Neither of the latter 2 patients have had sustained elevation of the blood urea nitrogen since termination of the thiosemicarbozone therapy or any other evidence of permanent renal damage. Albuminuria, microscopic hematuria, and cylindruria were present in small but significant degrees during therapy in these 2 patients and, to a greater extent, in the patient who died of amyloidosis. Similar urinary abnormalities were rare and transient in the other 4 patients who had no evidence of nitrogen retention.

One patient developed a two-plus cephalin flocculation test without other evidence of liver damage. Two patients had slight increase in the indirect van den Bergh reaction, from 0.2 to 1.0 and from 0.15 to 0.9, respectively. The values for these tests returned to the normal range after discontinuation of therapy. Two of these patients were among those who had severe anemia, and the disturbance may be a reflection of hemolysis.

No improvement was noted, either clinically or roentgenographically, in any of the 7 patients treated. Six had far advanced chronic fibrocavernous disease in which little objective improvement could be anticipated. Symptomatic improvement was conspicuously absent, however, in contrast to improvement in a group of similar patients who were treated with isoniazid. The sputum remained positive for *M. tuberculosis* by culture in all of the patients. *In vitro* tests of the drug susceptibility of the patients' tubercle bacilli were performed. The susceptibility of the pretreatment cultures was in the neighborhood of 1.0 γ of thiosemicarbazone per ml. of culture medium. Reduced drug susceptibility was demonstrated in several cultures of *M. tuberculosis* from patients treated longer than one month. The greatest change was to 5.0 γ of drug per ml. after eight weeks of treatment.

Among the 7 patients treated, 3 were chronic schizophrenics, 2 were chronic alcoholics with psychoses, one was psychotic with cerebral arteriosclerosis, and one had involutional melancholia. There was no change in their behavior or in their thinking disorders during the treatment.

In summary: Seven patients with chronic pulmonary tuberculosis were treated with *p*-isobutoxybenzaldehyde thiosemicarbazone for a four- to nine-week period. Anemia, presumably hemolytic, was observed in 4 of these patients. Other evidences of hematologic toxicity were not encountered in this small series. Nephrotoxicity in the form of renal irritation, which caused albuminuria, cylindruria, and microscopic hematuria, was observed in 2 patients, one of whom had a significant increase during therapy of a pre-existing nitrogen retention. A third patient with pre-existing renal damage from amyloidosis may have had some aggravation of a terminal uremia as a consequence of the therapy. Laboratory evidence of hepatic disturbance was observed in 3 patients, 2 of whom had anemia and in whom the abnormal findings may have resulted from hemolysis.

All of the toxic effects were apparently reversible. Evidence of symptomatic benefit was conspicuous by its absence, and no objective improvement was observed in this group of chronic far advanced cases of tuberculosis.

Franklin D. Roosevelt Hospital
Veterans Administration
Montrose, New York

Edward M. Garment
Joseph G. Epstein
Siegbert Bornstein
Mortimer Russell
Maurice Pachter

Department of Medicine
Cornell University Medical College
New York, New York

Carl Muchenheim

May 12, 1953

CLINICAL TRIAL OF PARA-ISOBUTOXYBENZALDEHYDE THIOSEMICARBAZONE IN EIGHT CASES OF TUBERCULOSIS

Since the advent of pyrazinamide and, of late, of isoniazid, much interest has been focused on synthetic antituberculous drugs, including the thiosemicarbazone series. One of these, the *p*-isobutoxybenzaldehyde thiosemicarbazone[1], was given clinical trial in 8 selected tuberculosis cases.

These cases represented 4 patients who had received maximum benefit from streptomycin–para-aminosalicylic acid (PAS) therapy and 4 patients who had not had the benefit of previous antimicrobial therapy.

In none of these patients was the tuberculosis suitable for collapse or surgical treatment at the time when the thiosemicarbazone therapy was institutued.

The present investigation was planned as a joint enterprise with investigators at the New York Hospital-Cornell Medical Center, and the two groups were in frequent communication with each other throughout the study. The results from the New York Hospital service are reported separately in this issue of the REVIEW (Muschenheim *et al.*, p. 791).

Eight patients, 3 male and 5 female, ranging in age from eighteen months to thirty-one years, were selected for treatment with the thiosemicarbazone. All had pulmonary tuberculosis from moderately advanced to far advanced in extent. Two patients were suffering from tuberculous meningitis, and one from extensive genitourinary tract tuberculosis. One patient was three months pregnant at onset of therapy.

Two of the patients had received 160 gm. of dihydrostreptomycin and daily para-aminosalicylic acid (PAS) simultaneously (Patients G. S. and W. B.). One patient had received 77 gm. of dihydrostreptomycin and daily PAS simultaneously which had been discontinued because of toxic symptoms (Patient W. J.). One patient (D. A.) had received 35 gm. of dihydrostreptomycin for meningitis immediately previous to the present studies. The remaining 4 patients had received no previous medication.

Before institution of therapy, each patient was studied clinically and by laboratory tests. These included physical examination, chest roentgenogram, complete blood count, erythrocyte sedimentation rate, determinations of hematocrit, nonprotein nitrogen, and serum bilirubin, urinalysis, and sputum or gastric lavage examinations for tubercle bacilli.

Initially, the patients were given 5 to 7 mg. per kg. per day. However, because of a report of granulocytopenia in one of the New York Hospital patients and the development of a severe anemia in one of the 8 patients of the present series, the dosage was reduced to approximately 2 mg. per kg. of body weight per day. The total daily dose was given in two divided doses every twelve hours.

Two patients (G. S. and C. W.) received isoniazid simultaneously in total daily doses of 4.5 and 6.5 mg. per kg., respectively.

The total duration of treatment ranged from ten to ten and one-half months in 4 patients, eight and one-half to nine months in 2 patients, and twenty-seven and twenty-four days in the remainder of the group.

Roentgenograms of the chest were obtained every month for follow-up purposes. The patients were seen daily and were observed for any untoward symptoms or signs.

Blood and urine studies included simple tests of the status of the hemopoietic, hepatic, and renal systems with the idea that further tests would be ordered if found necessary.

[1] The *p*-isobutyoxybenzaldehyde thiosemicarbazone was synthesized by and supplied through the courtesy of E. R. Squibb & Sons.

The results are divided into two groups. The first includes patients N. P. and C. W., who received therapy for only twenty-three and twenty-seven days, respectively. The second group includes the remaining 6 cases.

Group I

Patient N. P. developed a severe anemia within twenty-three days of treatment.

> There were rapid decreases in the erythrocyte count from 3.95 million to 1.6 million per cu. mm., in the hemoglobin from 12 gm. to 4 gm. per 100 ml., and in hematocrit readings from 28 to 15. There was a slow rise of serum bilirubin from 0.35 mg. to 1.4 mg. per 100 ml. and also a rise in the leukocyte count from 12,150 per cu. mm., with a differential of neutrophils, 77 per cent, and lymphocytes, 23 per cent, to 18,800 leukocytes with 92 per cent neutrophils and 8 per cent lymphocytes.
>
> Sternal marrow aspiration showed exaggeration both of granulocytopoiesis and erythropoiesis with increased proportion of immature cells of both series. In the granulocytopoietic series, there were distinctly increased numbers of mature and nearly mature granulocytes. The erythroid proliferation was normoblastic in type. There was no evidence of leukemia. An erythrocyte fragility test showed hemolysis beginning at 0.42 per cent solution and completed at 30 per cent solution. Coomb's test showed no titer of antibody. Tests for urine urobilinogen were negative.

There was no evidence of gross hemorrhage at any time. In view of the above findings, it was believed that the anemia was caused by the thiosemicarbazone, which affected the erythrocytes particularly.

The thiosemicarbazone was discountinued and, with blood transfusions and iron therapy, the hematologic findings returned to pretreatment values in approximately a month.

The patient showed no beneficial clinical results from the treatment received and progression of disease was noted on roentgenographic examination.

Patient C. W. was suffering from miliary and meningeal tuberculosis and tuberculosis of the left knee joint.

> This patient was acutely ill, with a daily temperature of 102°F., irrational, incontinent, and unable to eat or swallow at the onset of therapy. However, at the end of three weeks of thiosemicarbazone and isoniazid therapy, the daily temperature was normal, the patient became rational, continent, and was able to eat normal food.
>
> At the end of twenty-seven days of therapy, the family removed the patient from the hospital against medical advice. It was reported subsequently that this patient died at home.

Group II

Generally speaking, no dramatic results were seen in the remaining 6 cases. Two patients (R. L. and G. S.) experienced defervescence in two to four months. One patient continues to run a low-grade fever (W. J.), and the remaining 3 patients were afebrile at the beginning of therapy. One patient gained 19 pounds in weight (G. S.) and another, 10 pounds (R. L.); but 2 patients have lost 5 to 3 pounds during the thiosemicarbazone therapy. No dramatic change in appetite was seen in any of the patients except for the 2 who received isoniazid concurrently with the thiosemicarbazone. All the patients have shown reduction in the amount of cough and sputum, but in a very general manner. In one patient (R. L.), the sputum became negative for tubercle bacilli on culture.

In 4 patients, definite but slight to moderate roentgenographic improvement was

TABLE 1

Summary of Diagnosis and Treatment

NAME	AGE	SEX	DIAGNOSIS	TYPE OF LESION	COMPLICATION	PREVIOUS MEDICATIONS	ISONIAZID	THIOSEMICARBAZONE			
								Date	Length	Dosage	
										Daily	Mg. per Kg.
										mg.	
R. L.	21	F	Tuberculosis pulmonary, far advanced	Fibrocaseous cavitary	Pregnancy	None	None	May 7 to June 17	42 days	300	7 mg.
								June 18 to February 23	8 months+	100	2 mg.+
C. W.	31	F	Tuberculosis, pulmonary, far advanced	Miliary	Tuberculous meningitis, tuberculous knee	None	250 mg. per day, 6.5 mg. per kg.	May 7 to May 13	7 days	350	8 mg.
								May 14 to June 3	21 days	250	6 mg.
V. B.	20	F	Tuberculosis, pulmonary, far advanced	Exudative cavitary	None	None	None	May 20 to June 17	28 days	250	5 mg.+
								June 18 to March 23	10 months	100	2 mg.
N. P.	27	F	Tuberculosis, pulmonary, far advanced	Exudative cavitary	None	None	None	May 20 to June 13	24 days	250	7 mg.—
D. A.	18 months	F	Tuberculosis, pulmonary, primary	Exudative and atelectatic	Tuberculous meningitis	Streptomycin, 1 gm. per day, 35 days	None	May 20 to July 6	48 days	50	5 mg.
								July 7 to March 23	8 months+	25	2 mg.+
W. J.	15	M	Tuberculosis, pulmonary, far advanced	Fibrocaseous cavitary	None	Streptomycin 77 gm., plus PAS	None	May 27 to June 17	21 days	300	6 mg.
								June 18 to March 23	9 months	100	2 mg.
W. B.	22	M	Tuberculosis, pulmonary, moderately advanced	Fibrocaseous cavitary	Tuberculous kidneys, bladder, epididymis	Streptomycin, 160 gm., plus PAS	None	June 10 to June 17	7 days	350	7 mg.
								June 18 to March 23	9 months	100	2 mg.+
G. S.	24	M	Tuberculosis, pulmonary, far advanced	Exudative cavitary	None	Streptomycin, 160 gm., plus PAS	200 mg. per day, 4.5 mg. per kg.	July 1 to present	8.5 months	100	2 mg.

noted. In one patient (W. J.), however, definite progression of the disease occurred during the thiosemicarbazone therapy.

The erythrocytes were not affected except in one patient (W. B.), in whom there was a gradual and slow depression of erythrocytes, hemoglobin, and hematocrit. There was no tendency toward agranulocytosis in any of the patients. No elevation of esosinophils was noted. The erythrocyte sedimentation rate showed definite fall in 4 cases and remained normal in the other 2. The serum bilirubin value remained within normal limits in all cases.

Urinalysis failed to show any tendency toward renal damage. In the patient with extensive genitourinary tuberculosis (W. B.), urine studies and intravenous urogram remained unchanged. However, some diminution of pain and frequency were noted.

The patient (D. A.) who had tuberculous meningitis, for which she had received 35 gm. of dihydrostreptomycin, has continued to improve while on the thiosemicarbazone study. Clinically, she has a minor residual form of hemiparesis, but is otherwise well. The pre-therapeutic cerebrospinal fluid sugar concentration of 35 mg. per 100 ml. has gradually increased to 64 mg. per 100 ml.

One patient (W. J.) was receiving pneumothorax on the left side before and during his trial on thiosemicarbazone. Nine months after beginning this drug, he developed a pleural effusion on the side of his pneumothorax. It was apparently secondary to his collapse therapy.

In summary: Eight patients with pulmonary tuberculosis, 3 of whom had extrapulmonary complications, have been treated with *p*-isobutoxybenzaldehyde thiosemicarbazone for a period ranging from twenty-three days to ten and one-half months.

The over-all clinical, laboratory, and roentgenographic response to this drug was slow and gradual and was definitely not dramatic. There was only one case of sputum "conversion" by culture.

The one significant fact appears to be that the patient with meningitis has continued to improve without the aid of other antituberculous chemotherapy. No improvement was seen in a case of severe genitourinary tuberculosis either roentgenographically or by laboratory studies.

One case of severe anemia was noted after only twenty-three days of therapy. This was, however, not seen in the other patients even after ten and one-half months of therapy.

In the dosage given, which was approximagely 2 mg. per kg. per day, there was no evidence that the thiosemicarbazone affected the hepatic, renal, or nervous systems.

Obviously, no definite conclusions could be drawn from so few cases, but the antimicrobial efficiency of this drug would appear to be no better than that of para-aminosalicylic acid and possesses the added disadvantage of the capacity to produce hematopoietic toxicity.

United States Department of the Interior
Office of Indian Affairs
Tacoma Indian Hospital
Tacoma 5, Washington

Joseph J. Saia
K. Kasuga

Barton Memorial
Division, Jefferson
Medical College Hospital
Philadelphia, Pennsylvania

Joseph N. Aceto

March 27, 1953

Books

THE WHITE PLAGUE. By René and Jean Dubos. Pp. 277, Little, Brown & Co., Boston 1952, Price $4.00.

There have been innumerable books written about tuberculosis, many of them classics, but none is more fascinating than this volume by René and Jean Dubos. Dr. Dubos' recognized skill in writing, his many contributions in bacteriology and pathology, as well as numerous other attainments, make this volume all the more valuable and timely.

He has cleverly sketched the epitome of our knowledge of this disease over the ages so that the professional as well as nonprofessional worker or student can follow the dramatic scenes of the ages, as this disease has revealed itself to mankind for at least six thousand years. All tuberculosis workers should read and ponder its pages, and the majority of patients may benefit thereby; for, despite the seemingly never-ending tragedy, there has been, and will continue to be, hope if we but apply our knowledge intelligently.

The world is shrinking so far as man's ability to move from place to place is concerned. It becomes of the utmost importance, therefore, to recognize that there are approximately fifty million sufferers from this disease at any time, and that from three to five million people die every year. Thus, our ability in recent years to accelerate the decline of our tuberculosis death rates here in this country must be weighed against the millions of sufferers still in the world who are the source of a never-ending chain of new cases to plague us for decades to come.

The book is divided into four parts. In the first five chapters the authors deal with the "White Plague" in the nineteenth century. Few may realize that in 1699, the Republic of Lucca promulgated the first decree of prophylaxis. These regulations were specific and severe in their attempts to isolate the diseased person, and for many years were vigorously enforced. However, not all physicians of those days accepted the theory of contagion, and the strict application of the regulations was so costly that they were finally abandoned. It is of interest to recall that, in 1898, Hermann M. Biggs, in New York, was fighting a similar battle. The regulations he established at that time have been a pattern for health departments the world over. One may well wonder, if the edict of 1699 had remained in force throughout the years which have followed, if this preventable disease would not be much nearer control today. It is on this point that the authors have made a notable contribution to our knowledge of the disease. It is ". . . the subtle interplay between the social body and the social disease which constitutes the central theme."

In the second part, the authors discuss "The Causes of Tuberculosis" the germ theory, tubercle infection and disease, and the detection thereof. From the beginning of the eighteenth century, the possibilities of percussion and auscultation were recognized and continue to form a basis of our evaluation of changes in the chest, even though the chest X-ray discovered in comparatively recent times has today replaced this valuable technique in the minds of some.

Part three deals with "Cure and Prevention of Tuberculosis." Here the authors have winnowed out a significant amount of material from the vast reservoirs of writings on the subject. It is significant to note the emphasis placed on nutrition for decades, and yet to realize that in this day we still do not know precisely the part nutrients play in the behavior of infection and disease. One statement of the authors highlights the inter-relationship of this vast amount of study and observation: "It was clinical experience that revealed the therapeutic effort of healthy living, good food and rest in tuberculosis. But it took the

resources of physiological, pathological, bacteriological and chemical sciences to bring about the more active forms of treatment, such as pulmonary collapse, surgery and the use of antimicrobial drugs."

The final section deals with "Tuberculosis and Society—The Evolution of Epidemics, Tuberculosis and Industrial Civilization and Social Technology." It is in this broad field that we find such striking examples of the behavior of tuberculosis which seem to come about irrespective of changes associated only with exposure to the bacilli. "It seems that the severity of tuberculosis immediately reflects the complex of disturbances brought about in the community as a whole by most forms of racial upheavals, be they abrupt changes in ancestral habits, rapid industrialization or wars."

The concluding paragraph of this charming book has epitomized the problem admirably and points to the direction we must take to develop the resources essential to the final result:

> It is entertaining and reassuring to discover that the laborious efforts made by medical science to eradicate tuberculosis have confirmed the value of certain ancient practices. Instinctively, or empirically, many primitive civilizations had developed the art of achieving fitness between human urges and the natural environment. We need to develop a new science of social engineering that will incorporate physiological principles in the complex fabric of industrial society. It will be the enviable task of the future to reconcile the glamour of modern life with the ancestral wisdom of the happy savage.

Herbert R. Edwards
New York, New York

Chronic Pulmonary Emphysema: Physiopathology and Treatment. By Maurice S. Segal. Pp. 180, with tables and illustrations. Number 8 in Modern Medical Monographs, Grune & Stratton, New York, 1953, Price, $5.50.

During recent years a vast amount of new information has been accumulated about the derangements of pulmonary and cardiac function in chronic pulmonary emphysema. Scattered about in the medical literature in the form of fairly technical reports of investigations, this new knowledge is not readily accessible to the practitioner and student. Consequently, wide application of its therapeutic implications in the management of this very common pulmonary disease has been hindered. Implicit in this knowledge is the discrediting of the older teaching that emphysema is a slowly progressive irreversible disease characterized primarily by loss of lung elasticity—a notion responsible for widespread negativism in therapy.

The authors of this book have been eminently successful in correcting an untoward situation by bringing together in relatively few pages the modern concepts of the pathogenesis, physiopathology, and therapy of chronic pulmonary emphysema. They have stated these concepts in a form which would appear to be acceptable to most workers in this field which, because of its rapid advancement, is still fraught with considerable controversy. Particularly commendable is the emphasis placed on physiologically directed therapy in achieving partial or complete reversal of many of the functional defects and complications of the disease. They clearly summarize the evidence that the breathing ability of the patient with emphysema can be improved and that the seemingly inexorable progress of the disease to fatal respiratory failure or cor pulmonale may be altered by the enlightened physician. Conversely, the paradoxical role of the unenlightened therapist

in hastening the death of the patient by the overenthusiastic use of oxygen and sedation is appropriately discussed.

The book is not without its faults. In the important chapter on the carbon dioxide intoxication syndrome, the disturbances of blood carbon dioxide and pH levels, so commonly encountered in advanced pulmonary emphysema, could have been described with greater clarity. In this connection an increased excretion of chloride rather than the more directly significant augmented reabsorption of bicarbonate is frequently referred to as the compensatory response of the kidneys to an increase in blood carbon dioxide tension. A statement of the Henderson-Hasselbach equation and the inclusion of Gamble-type diagrams would improve this chapter greatly.

In the otherwise excellent chapter on pulmonocardiac complications, the statement that "aminophyllin can also serve as a means of evaluating the degree of reversibility of pulmonary hypertension" and that "lack of response to aminophyllin indicates a poor prognosis" has such inadequte evidence to support it that it is scarcely justified. In the appendix on methodology, the use of carbon dioxide in calculating the cardiac output by the Fick principle is presented as if it is in current use, whereas the notorious inaccuracy of this method has caused it to be abandoned a number of years ago. Also, in the appendix, the value for pulmonary vascular resistance is incorrect. Finally, a number of statements in the text are matched with the wrong references in the bibliography and a rare reference is misquoted. None of these faults can be considered grave and will undoubtedly be corrected in a subsequent edition.

This monograph is the most up-to-date and comprehensive work on pulmonary emphysema which is available between two covers. It should be required reading for students and practitioners.

DANIEL S. LUKAS
New York, New York

REHABILITATION OF THE PHYSICALLY HANDICAPPED. Second Edition. By Henry H. Kessler. Pp. 275, Columbia University Press, New York, 1953, Price $4.00.

Dr. Henry H. Kessler's revised second edition of a recognized standard work is patently not intended to be a technical treatise since, of its 275 pages, 55 are concerned with "Principles of Rehabilitation", which include only 10 pages on "Physical Restoration." The delineation, however, of general problems concerning the crippled child, the injured worker, the disabled veteran, the disabled due to chronic disease, the mentally and emotionally disabled, the orthopedic patient, the blind and the deaf, as well as the surgical and medical invalid, serves a very useful function in bringing these to the attention of nonspecialist medical and ancillary personnel and interested laymen. Dr. Kessler has drawn on his many years of personal experience in the field for this purpose.

The volume is especially useful in (*1*) tracing the development of civilian, veteran, and military rehabilitation efforts in this country; (*2*) outlining the legislative and administrative development at the local, state, and federal levels of interest in this field; and (*3*) providing in index form a list of the addresses of major rehabilitation centers and agencies concerned with the welfare of the handicapped.

There are those who would question the author's advocated principle of operating a rehabilitation center outside the framework of a general hospital. Modern medical rehabilitation experience has shown that the rehabilitant is to be considered primarily a patient with an underlying disease process, often systemic in nature. It is obvious that, in this light, there may be changes in the medical status of the patient during a rehabilitation

program which would require general hospital management. This consideration should also serve to point up the fact that rehabilitation is not a "para-medical" discipline since primary responsibility should be in medical hands.

In the section on rehabilitation of the tuberculous patient, no mention is made of post-surgical therapeutic exercises and other procedures which are being widely used in preventing skeletal deformity. These are well delineated in comprehensive tuberculosis rehabilitation programs. Also lacking in the section concerned with cardiovascular disease is reference to work classification units and other rehabilitation activities, recent developments intended as aids for rehabilitation in this group of patients. However, the author re-emphasizes a valuable point when he stresses the fact that the housewife with cardiovascular disease should be considered an important member of the working population. Finally, there are those who would take issue with the author in classifying patients with hemiplegia as the result of a cerebrovascular accident with those with orthopedic disabilities. It is well known that most patients with such cerebral insults have underlying disease of the cardiovascular system which necessitates the continuance of medical observation.

Dr. Kessler optimistically suggests that the problems of the physically handicapped may serve as common unifying threads for international understanding, a concept shared by others in the field.

The book is to be recommended for general informational purposes for all concerned with rehabilitation. The definitive technical textbook which includes consideration of current techniques and philosophies in physical medicine and rehabilitation has yet to be written.

Joseph G. Benton
New York, New York

BOOKS RECEIVED

Communicable Diseases. A Textbook for Nurses. Seventh Edition. By Albert G. Bower and Edith B. Pilant. Pp. 640 with illustrations, W. B. Saunders Company, Philadelphia and London, 1953, Price, $5.50.

Mass BCG Vaccination in Yugoslavia, 1948–1951, with special reference to Statistics on Tuberculin Testing and BCG Vaccination. Pp. 57, The International Tuberculosis Campaign, UNICEF, 24 Rue Borghèse, Neuilly-sur-Seine, France, 1952.

Mass BCG Vaccination in Morocco and Tangier, 1949–1951, with Special Reference to Statistics on Tuberculin Testing and BCG Vaccination. Pp. 41, The International Tuberculosis Campaign, UNICEF, 24 Rue Borghèse, Neuilly-sur-Seine, France, 1952.

Mass BCG Vaccination in Greece, 1948–1951, with Special Reference to Statistics on BCG Vaccination and Pre- and Post-Vaccination Allergy. Pp. 56, The International Tuberculosis Campaign, UNICEF, 24 Rue Borghèse, Neuilly-sur-Seine, France, 1952.

Studies on the Prophylactic Vaccine of Tuberculosis. By A. Imamura. Pp. 100, Osaka University, Osaka, Japan, 1952.

Memorias del Noveno Congreso de la Tuberculosis. July 14–22, 1951. Volume I. Pp. 409, Informes Oficiales Temas Nacionales, Guayaquil, Ecuador, 1953.

Les Accès Fébriles Périodiques des Tuberculeux. By Thérèse Ludwig. Pp. 41, Jouve & Cie, 15, Rue Racine, Paris, 1953.

Infectious Mononucleosis. By Sidney Leibowitz. Pp. 163, Grune & Stratton, New York, 1953, Price, $4.75.

EFFECTIVE INHALATION THERAPY. By Edwin Rayner Levine, Alvan L. Barach, J. Winthrop Peabody, and Maurice S. Segal. Pp. 157, National Cylinder Gas Company, Medical Division, Chicago, 1953, Price, $4.50.

MANUAL FOR FIELD WORKERS IN MASS BCG VACCINATION CAMPAIGNS. Pp. 58, United Nations International Children's Emergency Fund, 24 Rue Borghèse, Neuilly-sur-Seine, France, 1953.

MASS BCG VACCINATION CAMPAIGNS. A PRACTICAL GUIDE. Pp. 86, United Nations International Children's Emergency Fund, 24 Rue Borghèse, Neuilly-sur-Seine, France, 1953.

FOURTEENTH ANNUAL REPORT, 1952, THE TUBERCULOSIS ASSOCIATION OF INDIA. Pp. 208, 22, Talkatora Road, New Delhi-2, 1953.

PROCEEDINGS OF THE FOURTEENTH ANNUAL GENERAL MEETING OF THE TUBERCULOSIS ASSOCIATION OF INDIA. Pp. 27, 22, Talkatora Road, New Delhi-2, 1953.

PERSONALITY MANIFESTATIONS IN PSYCHOSOMATIC ILLNESS. By O. Spurgeon English. Pp. 57, Edward Stern and Company, Incorporated, New York, 1953, Price, $1.00.

ADVANCES IN VETERINARY SCIENCE. Volume I. Edited by C. A. Brandly and E. L. Jungherr. Pp. 431, Academic Press, Inc., New York, 1953, Price, $9.00.

SURVEY OF ANTIMALARIAL AGENTS. Public Health Monograph No. 9. By G. Robert Coatney, W. Clark Cooper, Nathan B. Eddy, and Joseph Greenberg. Pp. 323, Public Health Service, Federal Security Agency, Washington, D. C., 1953, Price, $1.25.

The Award of the Trudeau Medal for 1953

The Trudeau Medal for 1953 was awarded to Dr. James J. Waring at the annual meeting of the National Tuberculosis Association. The presentation was made by Dr. J. Burns Amberson as follows:

DR. AMBERSON: The man whom we have chosen to honor today because of his contributions to the campaign against tuberculosis is Dr. James J. Waring. He entered upon his career in medicine as a student at Johns Hopkins in 1904, the year of the birth of our National Tuberculosis Association. This concidence would be less than interesting were it not that, three years later, tuberculosis laid its heavy hand upon him; placed its mortgage on his future; and destined him to be one of our most faithful, influential, and effective allies. The cost of the conversion was the shattering of a young man's immediate hopes and dreams and the exactions of mental, emotional, and physical suffering which go with relapsing disease and many years on the "cure." The effect of adversity on his high spirit can well be understood, and there was a period of rebelliousness and depression. But the stroke of fortune also brought him as a patient and disciple under the influence of men who helped make our Association great—Edward L. Trudeau, Brown, Baldwin, Price, Webb, and Sewall. To be intimately touched by these personalities was indeed a compensation. Think of the solace conveyed in that letter from Trudeau written to young Waring at Christmas, 1907:

> . . . I have lived much longer however than you have and have learned that many of the things we so repine at losing are really of little moment, are unenduring and unsatisfying and that to know God in our hearts is what really matters most in this life. I have seen souls grow while bodies shrivel and the really great things of life unfold to a man when all that the world prizes most has been denied him . . .

Such were the circumstances which molded the life and character of Waring into that of a great, good, and humane physician. Taking up the broken thread of his career at the University of Colorado, he finally received his medical degree and, in turn, he eventually served there as Professor of Medicine from 1932 until 1952. Through him as a teacher was projected the inspiration and understanding of the men who were his physicians and advisors. During these twenty years and more, hundreds of students in their formative and impressionable years came to his clinics and classes, where they received not only a knowledge of facts, skills, and techniques but also a fine indoctrination in the art of medicine. With vivid recollections from his own experience of the qualities most to be desired in a physician and a lasting sense of gratitude for the widsom and understanding which tuberculosis, as the disguise of Fate, had enabled him to achieve, he imparted to these young people a conception of their obligations which surely is redounding to the benefit of patients, whatever may be the form of their suffering. Knowing as we do that one of our most effective instrumentalities against tuberculosis is the interested, competent, broad-minded, and devoted physician, we can say that Waring, besides giving directly of himself, has multiplied himself many hundredfold and thus has extended his beneficent influence far beyond the limits set for the average man.

To the bedside of the sick patient Dr. Waring brings, not only a knowledge of modern

medicine, but also a fine sense of relative values. In 1936, as the President of the Association, he offered the following commentary on physical diagnosis:

> Are centuries of bedside experience assembled by thousands of observers to be tossed to oblivion while we choose the will-o'-the-wisp of the x-ray through the unreal land of lights and shadows? The answer is No! The history of physical diagnosis teaches us that nothing good is ever lost. Auscultation increased the value of percussion; roentgenography increases the value of both. Let the slogan of the stethoscopist be: Listen, look and listen again.

He has always advocated and exemplified breadth of view and of training because this ensures the best service to the patient. It also guards against errors which threaten in times like the present, when the onrush of new developments in the treatment of tuberculosis may be too narrowly judged through the quick and easy medium of the X-ray film. We need stout champions, like him, of that which is good in the old as well as that which time may prove to be good in the new.

Human understanding, compassion, and humility in the physician are highly valued by patients, as well as by healthy humanity—often far more than other attributes. When, as in Dr. Waring, they dominate the actions and services of a man who is also a scholar, a student of science, a skilled practitioner, and an excellent teacher, there is reason for special gratitude and honor. These qualities are intangible and one should not pretend to estimate them with finality. Nonetheless, they add deep meaning and sound merit to the purposes to which this man has given so much of his thought and effort. For all we know, they may count as much as the discovery of a new technique or a new medicine. If a patient is inspirited while being healed and a student is inspired while being instructed, the world should be even more the gainer.

In his presidential address before this Association in 1926, Theobald Smith, referring to the high cost of health, had this to say:

> But we cannot have the purchase money for this as well as for many other activities. We must choose and make sacrifices. We cannot raise ourselves to a level of health and stay there without continual effort. We are, in fact, perpetually mortgaged to health.

At the start it was said that, in 1904, tuberculosis placed a claim on the career of James J. Waring, even before he became a physician. As he retired from the Chair of Medicine in Colorado a year ago, the claim was renewed and he carried on as President of the Board of Trustees and Director of Research of the Colorado Foundation for Research in Tuberculosis. Only several weeks ago the cornerstone of the building to house this activity was laid in Denver. It is to be a memorial to Gerald B. Webb, one of our late presidents.

Since "we are . . . perpetually mortgaged to health," it is fortunate that our investment is placed, not only in fine institutions and facilities, but also in men like Doctor Waring. The pattern of his ideals reflects that of the physicians who steadied and inspired him; in turn, it has made its imprint on the lives and careers of patients, students, physicians, and many others devoted to the fight against tuberculosis. The Trudeau Medal symbolizes our grateful recognition of the service he has given our cause.

DR. WARING: I feel woefully inadequate to say to you what lies in my heart. Indeed, I scarcely dare try for fear one of these high fogs will come up in my throat.

To receive this award from the hands of Dr. Amberson also adds greatly to my happiness. He has treated me more generously than I deserve!

Nearly fifty years ago Dr. Lawrason Brown said to me: "The day will come when you will be glad you had tuberculosis." I raged at him with impatient incredulity. Long since I admitted to him that he was right. In my very first interview with Dr. E. L. Trudeau, he said to me: "It takes a bit of the Divine Fire to get well of tuberculosis." Kingston Fowler, a great British doctor, phrased it a bit differently when he said: "No fool ever gets well of tuberculosis." They both meant the same thing.

I hope some of you have read the letter Dr. Trudeau wrote me in December, 1907, the first Christmas I spent at Saranac. You will find it in the Baldwin Memorial Issue of the AMERICAN REVIEW OF TUBERCULOSIS. This letter embodies the magnificient spirit of a great doctor and exemplifies the spirit that pervaded Saranac, indeed that pervades Saranac and Trudeau to this day. My debt to Trudeau, Brown, Baldwin, Price, David Lyman, Dr. Hatfield, and others still alive today can be discharged only at the bedside "to cure sometimes, to comfort always."

When I came West, I was fortunate to come under the eye of Gerald Webb and Henry Sewall, who were my sponsors in baptism wherein I was made a member of the National Tuberculosis Association and an inheritor of certain responsibilities in relation to Webb's Foundation for Research in Tuberculosis. I am glad to tell you that a building to be known as the Gerald B. Webb Memorial Building is now being constructed at the Medical Center in Denver and will house Webb's Foundation for Research.

Twenty years ago the annual meeting of the NTA was a very quiet, pleasant affair. Some sound clinical and laboratory reports, much activity on the part of the nonmedical group, an evening or two of bridge with Jim Miller, Gerald Webb, David Lyman, Charles White, and that was all. Compare that with the wonderful program we have had here on this occasion. I feel like jumping into the middle of the aisle and shouting "Hallelujah! Bless the Lord."

But, we have only a distant view of the promised land of eradication of tuberculosis. Much remains to be done. We need desperately to know whether drug-resistant organisms recovered from resected lungs have permanently lost their pathogenic properties for man. Whether others are truly irreversibly dead or only slyly sleeping awaiting their opportunity to jump out into the bronchial aisle and shout "Hallelujah! I was only fooling." We need to know whether the future of patients who have had lesions resected is less hazardous than if these lesions had not been resected. We need to know whether primary tuberculosis in child and in adult should be treated with chemotherapy. We need to know whether the recent converter of the tuberculin test from negative to positive should have chemotherapy. We need to re-appraise bed rest, that healer of wounds but sometimes wearisomely prolonged, a destroyer of morale, and an inciter of insubordination. These and many other problems clamor for solution.

Time was when the campaign against tuberculosis was waged by a handful of sanatorium doctors and an army of nonmedical workers from all parts of the country. The complexion of the campaign today is different, and the change is due to the progress of thoracic surgery and the stimulating influence of chemotherapy. The present meeting, with its large number and variety of fine papers and many doctors in attendance, illustrates my point.

The army of nonmedical workers which has carried the fight in the public health plan for so many years is now being reinforced by a surging tide of young doctors fighting hand to hand with the foe at the bedside, in the operating room, and in the laboratory.

The medical section of the NTA was never so sturdy, never before had so much to offer in the fight as now. This simply means that never before was the NTA so strong.

One word more and I am done! Some fifty years ago we had in Denver a fine Dr.

Bancroft. He weighed some 350 pounds. Many good stories revolved around his name. On one occasion he was called in consultation by a young colleague. After examination of the patient, he asked the young doctor what he was doing for the patient. Thereupon, he was shown the many boxes and bottles on the bedside table. After a review of this amazing array of remedies for every conceivable symptom, Dr. Bancroft said, "Son! I don't see that you have left anything for God Almighty to do for this patient."

Surgery cannot remove all tuberculous disease from the patient, something is always left behind for God Almighty to take care of.

Over the portal of the new Webb Building in Denver will be carved three Latin words meaning, "Work and hope."

Report of the Committee on Medical Research, 1952—1953

The Committee on Medical Research and its subcommittees held nine meetings during the year, as follows:

Committee on Medical Research, Joint Session with Investigators, October 8 and 9, 1952.

Committee on Medical Research, Executive Session, October 9 and 10, 1952, and May 16, 1953.

Laboratory Subcommittee, Dr. Gardner Middlebrook, Chairman, October 7, 1952, and May 15 and 16, 1953.

Fellowship Board, Dr. J. Burns Amberson, Chairman, October 7, 1952, and May 16, 1953.

Joint Sessions, Laboratory Subcommittee and Committee on Therapy, October 7, 1952, and May 16, 1953.

Activities of the Committee on Medical Research

At the fall meeting, 27 research grants were recommended for approval by the Committee on Medical Research. One was later withdrawn. Twenty-six grants were acted on favorably by the National Tuberculosis Association Board of Directors at its meeting February 13 and 14, 1953. The total amount awarded for these grants was $149,140.

At the spring meeting, May 16, eleven awards, one supplementary award, and one provisional award were recommended for approval, at a cost of $43,724. These recommendations received favorable action by the NTA Board of Directors at its meeting on May 20. (Since then, through correspondence with investigators concerned, the chairman of the Committee, the Director of Medical Research, and the comptroller of the NTA, one award has been withdrawn and necessary adjustments have been made in certain others. The final total cost of 37 grants and one supplementary grant is $194,626.) During the year, seven applications for grants were not approved after careful consideration by the Committee.

As in the past, the research recommended for support covers a wide range of problems in tuberculosis and a few in closely related diseases. The major emphasis is on the pathogenesis of tuberculosis, the problems of immunity and allergy, and the pathogenetic mechanisms of the tubercle bacillus. Other fields of study include genetics of *Mycobacteria*, constitutional factors in resistance, pulmonary physiology, and the effects of various types of treatment.

The Committee reviewed a number of applications under consideration by constituent associations for assistance on a state or local level. The practice of submitting such applications for the opinion of the Committee on Medical Research has been followed for several years and has been helpful to tuberculosis associations in their efforts to make the best possible choice of projects to be supported.

During the year the Committee revised the grant application forms and information sheet. This was done to improve the usefulness of the forms for administrative purposes and to ensure the availability of all the information required in judging the merits of each application.

The Committee also reviewed the NTA policy on payment of funds to the institution in which supported research is conducted and its policy with regard to progress reports from investigators and financial statements. The current practice requiring a progress report twice a year was considered a good one, but the Committee thought that every effort should be made to reduce the number of financial statements, now four a year, to a

minimum. The Director of Medical Research was asked to take this question up with the NTA comptroller.

In view of changing trends in the patent policy followed by a number of universities and institutions engaged in medical research in this country, the Committee considered the NTA patent policy which was adopted in 1940 and has been followed since. The question was thought to be one requiring most careful consideration, as well as inquiry into policies acceptable to other grant-awarding organizations. The Chairman of the Committee appointed a subcommittee to investigate further and make recommendations to the full committee at its next meeting.

Finally, the Committee approved the principle of naming a limited number of fellowships and grants for a period of one year or longer in honor of persons who have made generous bequests to the NTA. This has been done in the past for a few fellowships and is considered an appropriate method of giving recognition to some bequests which have not yet been allocated for a specific purpose.

Activities of the Laboratory Subcommittee

The activities of the Laboratory Subcommittee of the Committee on Medical Research will be reported separately in the American Trudeau Society section of THE AMERICAN REVIEW OF TUBERCULOSIS in the December issue.

A list of grants-in-aid of research awarded for establishment during the 1953–1954 fiscal year follows:

Research Grants Approved for Establishment During Fiscal Year 1953–1954

Investigator	*Location of Research*	*Title of Research*
Rudolph J. Anderson	Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut	Chemistry of tubercle bacilli
Theodore L. Badger	Boston City Hospital, Boston, Massachusetts	Studies in pulmonary physiology
Emil Bogen	Olive View Sanatorium, Olive View, California	Classification of *Mycobacteria*
Vernon Bryson	Biological Laboratory, Cold Spring Harbor, New York	Genetics of *Mycobacteria*
Paul A. Bunn	State University of New York, Syracuse, New York	Use of the rabbit eye as a tissue for study in experimental tuberculosis
Mary I. Bunting	Brady Laboratory, Yale University, New Haven, Connecticut	Genetics of *Mycobacteria*
Amos Christie	Vanderbilt University, Nashville, Tennessee	Pulmonary calcification in fungus diseases
Carl Cohen	Jackson Memorial Laboratory, Bar Harbor, Maine	Propagation of rabbit stocks of known resistance to tuberculosis
Sidney P. Colowick and Nathan O. Kaplan	McCollum-Pratt Institute, Johns Hopkins University, Baltimore, Maryland	Mechanism of action of isonicotinic acid hydrazide

John E. Forney	University of Southern California, Los Angeles, California	Allergy and serology of tuberculosis
Bruno Gerstl	Veterans Administration Hospital, Oakland, California	Humoral antibodies in tuberculosis
Alfred Goldman	City of Hope, Duarte, California	Electrolytes, blood volume, protein partition and adrenal function in tuberculous and normal tissues of the tuberculous patient
David M. Gould	Johns Hopkins Hospital, Baltimore, Maryland	Production of teaching films on chest diseases
K. Albert Harden	Howard University, Washington, D. C.	Chronic pulmonary disease, lung surgery, and cardiac function
Waldemar F. Kirchheimer	Northwestern University, Chicago, Illinois	Correlation of mycobacterial enzyme and growth inhibition
Vernon E. Krahl	University of Maryland, Baltimore, Maryland	Structure of mammalian lung
Edith M. Lincoln	New York University-Bellevue Medical Center, New York, New York	Tuberculosis in children
Max B. Lurie	Henry Phipps Institute, University of Pennsylvania, Philadelphia, Pennsylvania	Genetic resistance to tuberculosis
Walsh McDermott	New York Hospital-Cornell Medical Center, New York, New York	Host-parasite relationships in tuberculosis
Gordon M. Meade and Roger S. Mitchell	Trudeau Sanatorium, Trudeau, New York	Statistical study of treatment in tuberculosis
Gardner Middlebrook	National Jewish Hospital, Denver, Colorado	Chemotherapy and pathogenesis of experimental tuberculosis
Quentin N. Myrvik	University of Virginia, Charlottesville, Virginia	Role of tuberculo-inhibitory factors in host resistance to tuberculosis
National Society for Medical Research	Chicago, Illinois	Annual contribution to educational program on scientific animal experimentation
Carroll E. Palmer	Division of Chronic Disease and Tuberculosis, Public Health Service, Washington, D. C.	Minimal tuberculosis in nurses
Emanuel M. Papper	Columbia University, College of Physicians and	Effects of anesthesia during pulmonary resection

	Surgeons. New York, York, New York	
Hilda Pope	Duke University, Durham, North Carolina	Metabolism of tubercle bacilli
Sidney Raffel	Stanford University, Stanford, California	Immunity and allergy in tuberculosis
Florence B. Seibert	Henry Phipps Institute, University of Pennsylvania, Philadelphia, Pennsylvania	Antigens of the tubercle bacillus
William Steenken, Jr.	Trudeau Laboratory, Trudeau, New York	Maintenance of Culture Depot
Vernie A. Stembridge	University of Texas, Galveston, Texas	Statistical study of pathologically proved tuberculosis
Kornel Terplan	University of Buffalo; and Laboratories of Niagara Sanatorium, Lockport, New York	Pathogenesis of tuberculosis and significance of old encapsulated lesions
Arthur J. Vorwald	Saranac Laboratory, Trudeau Foundation, Saranac, New York	Effect of inhaled silica on attenuated tubercle bacilli
Dwain N. Walcher	Indiana University, Indianapolis, Indiana	Evaluation of streptokinase-streptodornase in tuberculous meningitis
Charles Weiss	Albert Einstein Medical Center, Northern Division, Philadelphia, Pennsylvania	Caseation and softening in tuberculosis
H. Stuart Willis	North Carolina Sanatorium McCain, North Carolina	Studies in vaccination against tuberculosis
Richard J. Winzler	University of Illinois, Chicago, Illinois	Mucoproteins in human plasma
George W. Wright	Trudeau Foundation, Saranac Lake, New York	Pulmonary function studies

Respectfully submitted,

WILLIAM E. ADAMS
J. BURNS AMBERSON
ROBERT J. ANDERSON
HUGH E. BURKE
ANDRE F. COURNAND
ROBERT H. EBERT
H. CORWIN HINSHAW
LAWRENCE B. HOBSON
MAX B. LURIE
GARDNER MIDDLEBROOK
DAVID T. SMITH
WILLIAM STEENKEN, JR.
ARTHUR M. WALKER

KARL F. MEYER, *Chairman*

Report of the Fellowship Board of the Committee on Medical Research, 1952—1953

The Fellowship Board met twice during the year, on October 7, 1952, in New York City, and on May 16, 1953, in Los Angeles. At the main meeting in the fall, eight medical research fellowships were recommended. Included were two fellowships to be awarded and administered by the Medical Fellowship Board of the National Research Council, in accordance with an agreement made previously. In addition, two teaching-resident fellowships were reviewed at the request of the Committee on Medical Education; both were approved. The total cost of the medical research fellowships for the 1953–1954 budget was $20,350. In addition, $6,000 was transferred to the Committee on Medical Education for use in the teaching-resident fellowship program. One applicant withdrew, and one requested a shortened term.

At the interim meeting in the spring, four new medical research fellowships and two short-term were recommended at a cost of $12,514. The total cost of the 14 medical research fellowships recommended at both meetings amounted to $35,599. Subsequently, establishment of these fellowships, most of which will begin during the 1953–1954 fiscal year, and the transfer of $6,000 to the medical education budget, were approved by the Committee on Medical Research and the Board of Directors of the National Tuberculosis Association. (Since the meetings, one fellowship has been withdrawn and the cost of another reduced, making the net cost of 13 fellowships $32,085.) Five applications reviewed by the Fellowship Board at one or the other of the meetings were not recommended for approval.

The Board took up the question of publicity for the fellowship program at both of its meetings. In the fall, it was thought that wider publicity was needed as the number of applicants has usually not greatly exceeded the number of fellowships which could be awarded and there has been a narrow field within which to make a choice. During the late fall and winter, however, an unusually large number of inquiries about National Tuberculosis Association fellowships were received, and it was learned that an announcement of the NTA fellowship program had been distributed by the Division of Research Grants and Fellowships of the Public Health Service. Most of the inquiries were from students seeking financial support to further their basic scientific education; very few were from trained or nearly trained young investigators interested in devoting their careers to research in the field of tuberculosis or other pulmonary disease. The Board viewed this as a sign that wider publicity alone would not be helpful, as it brings a deluge of applications from persons who are not qualified and does not raise the standards of the program. The Board decided to circulate a poster to various medical schools and graduate schools throughout the country announcing the availability of National Tuberculosis Association medical research fellowships and defining their purpose and the qualifications required. Beyond this, the Board believes the only publicity which will serve the right purpose is that which is incorporated in the American Trudeau Society notes published in the AMERICAN REVIEW OF TUBERCULOSIS and in the National Tuberculosis Association and ATS Newsletters. The members of the American Trudeau Society should be well acquainted with the fellowship program and are in the best position to stimulate the interest of applicants who have the scholastic qualifications and an interest in the problems of tuberculosis.

The Board also reviewed the current policy on stipends for research fellowships, comparing the range for NTA fellowships with that of other fellowship-granting agencies, such as the National Research Council and the National Science Foundation. Compared with the stipends of these organizations, the NTA stipends for predoctorate fellowships

are considerably higher, and for post-doctorate fellowships somewhat lower, especially for the married Fellow with children. The Board agreed that more liberal dependency allowances are in order for married Fellows, while any change in the stipend range for unmarried Fellows, particularly at the predoctorate level, should be in the direction of reducing the amounts awarded. It was recommended that the range of stipends be raised to $3,000–$3,600 for postdoctorate Fellows designated at the 1953 spring meeting of the Committee on Medical Research and that the entire stipend policy be revised at the next main meeting of that Committee in the fall of 1953.

The application form and accompanying information sheet pertaining to medical research fellowships were revised, with a view to making the information given and sought as specific as possible.

Finally, as part of the general stock-taking that went on during the year, the Board prepared a questionnaire to be sent to all former medical research Fellows of the NTA. The questions have to do with the professional activities and achievements of former Fellows. It is hoped that the responses will indicate how successful the program has been in furthering the cause of medical research in tuberculosis.

The Board approved the principle of naming fellowships in honor of persons who have left bequests to the National Tuberculosis Association.

The Medical Fellowship Board of the National Research Council reported on the tuberculosis fellowship program administered by the Council with funds contributed by the National Tuberculosis Association. Since the inception of the program in 1951, $33,600 has been made available. Approximately $24,000 has been spent or is committed, and approximately $9,000 is to be allocated for 1954–1955. Three Fellows have been appointed in the program for a total of five fellowship years, and a fourth Fellow will begin in July, 1953. All of the Fellows are of the highest caliber in the opinion of the Fellowship Board.

Fellowships Approved for 1953–1954

Fellow	*Location and Supervisor*	*Title of Research*
A. J. Crowle	Stanford University Stanford, California Dr. Sidney Raffel	The immunizing factor of the tubercle bacillus
Donald D. Daniels	University of California San Francisco, California Dr. Ellen Brown	Pulmonary function studies
L. Ruth Guy	Stanford University Stanford, California Dr. Sidney Raffel	Oxygen tension as a factor in virulence of the tubercle bacillus and immunity to it
Jean Ellen Hawkins	Duke University Durham, North Carolina Drs. David T. Smith and Hilda Pope	Metabolism of virulent and avirulent *Mycobacteria*
Nelda B. Holmgren,	Northwestern University Chicago, Illinois Dr. Guy P. Youmans	Metabolism of virulent and avirulent *Mycobacteria*
Oris Burton Houglum	University of Washington Seattle, Washington Dr. Russell S. Weiser	Nature of bacterial surface of *Mycobacteria* in relation to lysozyme resistance

Irving Krasnow	University of California Medical School Los Angeles, California Dr. Emil Bogen	Physiological behavior of *Mycobacteria* species as an aid in their identification, differentiation and classification
Edward M. La Fond	Glen Lake Sanatorium Oak Terrace, Minnesota Drs. W. B. Tucker, R. H. Frost, E. T. Evans, and E. P. Fenger	Statistical analysis of clinical aspects of 300 cases of skeletal tuberculosis before advent of streptomycin
National Research Council	Washington, D. C. Candidate to be chosen by NRC Medical Fellowship Board	Research project at choice of applicant
National Research Council	Washington, D. C. Candidate to be chosen by NRC Medical Fellowship Board	Research project at choice of applicant
Edward M. Sewell	Children's Chest Clinic, New York University-Bellevue Medical Center New York, N. Y. Dr. Edith M. Lincoln	Therapy of tuberculosis in childhood
Helen Wago	New York University New York, N. Y. Dr. Vera S. Fry	Attitudes of registered professional nurses toward tuberculosis nursing
Joseph W. Whalen	Michigan State College East Lansing, Michigan Dr. W. L. Mallman	Problems in detection and isolation of *M. tuberculosis* in pathological material

Respectfully submitted,

ROBERT G. BLOCH
H. DUMONT CLARK
RUSSELL H. FROST
JOHN H. SKAVLEM
H. MCLEOD RIGGINS

J. BURNS AMBERSON, *Chairman*

Present Concepts of Antimicrobial Therapy in Pulmonary Tuberculosis

Report of Panel Discussion Held at the Annual Meeting of the American Trudeau Society, Los Angeles, California, on May 19, 1953

Walsh McDermott, *Chairman*

DR. MCDERMOTT: The session this afternoon is entitled "Present Concepts of Antimicrobial Therapy in Pulmonary Tuberculosis." We are delighted that the word "concepts" is in there because, if there is a unanimity of opinion among this panel, we will all be very much amazed.

I think we might as well start by introducing the members of the panel: Dr. Nicholas D'Esopo of West Haven, Dr. John C. Jones of this city, Dr. Ross McLean of Baltimore, Mr. William Steenken of Trudeau, Dr. Carl Tempel from Denver, and Dr. Guy Youmans of Chicago.

A year ago we were all pretty much occupied with a study of isoniazid and there were two questions about isoniazid to which we did not know the answers a year ago.

These two questions were: (*1*) How did it compare with streptomycin-PAS, and (*2*) Was it a short-term therapy or was it something which could be counted upon in the individual patient for the long pull? Carl, how do you feel about that now?

DR. TEMPEL: I think that we can say that streptomycin and isoniazid are quite comparable in their effectiveness; in fact, a good way to express that would be to say that I think they're about equal in usefulness in the treatment of tuberculosis.

DR. MCDERMOTT: How do you feel about it, Ross?

DR. MCLEAN: I think it's just a little early, even this year, to credit isoniazid in combination with either PAS or streptomycin with a position of equal therapeutic efficacy with combined streptomycin and PAS. I am quite aware that the British Medical Research group and the Public Health Service studies show that, if anything, it is slightly superior. But I would like to draw attention to the fact that these are observations during the first several months of treatment and that we have a good combined streptomycin-PAS experience behind us from which we are now beginning to get some idea of the really long-term effectiveness and the durability of results with streptomycin-PAS.

DR. MCDERMOTT: Durability? You mean during treatment or after?

DR. MCLEAN: After treatment. I don't think we know much about what's going to happen to these patients when they are taken off treatment and, therefore, hesitate to ascribe complete therapeutic equivalence at this point.

DR. MCDERMOTT: Nick, how do you feel about it?

DR. D'ESOPO: I agree entirely with Ross that in the initial phases INH and streptomycin look as good as streptomycin-PAS, but we do have three years' follow-up now with streptomycin-PAS and I think it will be some time before we can make comparisons. The two principal observations we need are the effect of streptomycin-INH on cavity closure and, secondly, the effect of this regimen on the viability of organisms in closed lesions.

DR. MCDERMOTT: John, it isn't strictly your responsibility to follow these things but you must see a number of patients who have the two forms of treatment. How do you feel about it?

DR. JONES: Well, I think the acid test for isoniazid is in those situations in which a surgeon is forced to operate on a patient whose organisms are resistant to streptomycin. In the few cases where we have had to depend on isoniazid, I'd say it does measure up.

DR. MCDERMOTT: Bill?

MR. STEENKEN: Mine will have to be from the animal side. In rabbit studies we have produced miliary tuberculosis which has been demonstrable by X-ray, and then treated them with the drug for long periods of time, say six months or a year, and then have removed the animals from the drug. We have not seen any relapse and this corresponds to the results we got when we were using streptomycin alone. So, on the animal basis, I think we can say that the relapse rate after prolonged therapy with the drug alone is no different than with streptomycin; in fact, it looks very good.

DR. MCDERMOTT: Ross, you mentioned that the results were early in the USPHS studies. Without anticipating yours and Dr. Chapman's papers too much on Friday, actually the USPHS study has gone forty weeks now, hasn't it?

DR. MCLEAN: I'm not exactly sure. I believe that's quite right.

DR. MCDERMOTT: That's nine to ten months.

DR. MCLEAN: With respect to the isoniazid regimens which were given alone, the Veterans' study ranges up to fourteen months. Our combined regimens in the Veterans' study range up to eight or nine months.

DR. MCDERMOTT: Well, now, on the first question I haven't polled Dr. Youmans yet; I'm saving him. The first question is: How does isoniazid compare with streptomycin or streptomycin-PAS in terms of antituberculous activity? And I would say that the opinion of the panel could perhaps be characterized by a rather pallid approval of isoniazid in comparison with streptomycin-PAS. Certainly today everybody seems to agree they're in the same class. Bill Steenken says that from the animal standpoint isoniazid is at least as good. That's your conclusion, Bill? Well, how about the other question: Is it good for the long pull or isn't it? Ross, do you have any figures on that?

DR. MCLEAN: First of all, with respect to relapses occurring during the course of treatment, there have been very few on any regimen. In the material I'm most familiar with, they have been least on combined streptomycin-PAS and most on INH alone.

DR. MCDERMOTT. That's the VA study?

DR. MCLEAN: Yes; and intermediate on the combined isoniazid-streptomycin, isoniazid-PAS.

DR. MCDERMOTT: And we're talking relapse detected by roentgenographic evaluation?

DR. MCLEAN: Or bacteriologic evaluation.

DR. MCDERMOTT: Lumping both together?

DR. MCLEAN: Lumping them both together for purposes of this informal discussion. They're both very infrequent and the least frequent of all are the streptomycin-PAS cases.

DR. MCDERMOTT: Well, that gets us into the subject of PAS. I must confess I don't quite agree that one can lump bacteriologic relapse and roentgenographic relapse, as measurements of drug, but I'll shoot this one at Guy Youmans. Guy, what is your opinion on the effects of PAS on the emergence of streptomycin-resistant tubercle bacilli?

DR. YOUMANS: Well, I don't think there's any question but what PAS certainly inhibits the appearance of streptomycin-resistant tubercle bacilli in patients. I think there is some question whether one can reproduce this phenomenon experimentally—at least, we were unable to do so. PAS, I think, definitely does prevent the emergence of streptomycin-resistant tubercle bacilli.

DR. MCDERMOTT: Then is it fair to say that it prolongs the period of streptomycin action?

DR. YOUMANS: It certainly should, yes.

DR. MCDERMOTT: Is there general agreement on this point, Ross? Do you all agree to that? Do you agree to it, Carl? Bill?

MR. STEENKEN: Well, I think it does in certain types of cases such as a cavitary case in

which the cavity has responded and comes down to the so-called closed type of lesion; but, if it remains an open cavity and you do not get conversion, you sure do get emergence of resistant organisms.

DR. MCDERMOTT: I think that's a very good point, Bill. Have you any notion, out of 100 patients with cavitary lesions which would persist for one year, who would receive streptomycin-PAS daily for one year—have you any notion on a hypothetical basis how many of them would be discharging predominantly streptomycin-resistant cultures?

MR. STEENKEN: I think Nick can answer that because he's been close to that part and he knows more about how his patients react. All I know is from specimens I receive, but I don't know the percentage.

DR. MCDERMOTT: How about it, Nick?

DR. D'ESOPO: I think, if you had 100 patients who were treated for a year and at the end of that time had open cavities and positive cultures, that just about all of them would have streptomycin-resistant organisms.

DR. MCDERMOTT: Carl, would you speak to that point?

DR. TEMPEL: I think—our experience has been, as you know, with the intermittent regimens and I'd rather give it on that basis, if I may. I think that up to eight months on those regimens of either SM or PAS or SM and INH, the conversion rate is very high so that you would only have a small number of positive cultures to test. The conversion rate would certainly be in the neighborhood of 80 to 90 per cent on either regimen at that point. But the majority of the cultures which were obtained at that point, I would say, would be sensitive to streptomycin or INH. After that point, it has been our experience that the trend is toward the resistance; but the significance of the whole thing is that there is such a small percentage of the entire group which shows this that it may be that after eight or twelve months only 10 per cent of your cases would have such resistant organisms. Up to eight months it's been less than 5 per cent, so that the fact of resistance in long-term combined intermittent streptomycin with either PAS or INH is not a very serious problem. The fact, as Nick told you, that, with the use of both drugs daily, so much resistance does occur seems to me to point up another factor to the advantage of the combined intermittent regimen. We would have more patients sent home having sensitive organisms than we would by the other method. I believe in our discussion of toxicity later that we can show that that factor, too, will all be in favor of this regimen, so that I think we can safely use these programs of treatment eight to twelve months with very small danger of resistance. At least, in those patients who require definitive long-term therapy, that's not a very serious problem at the moment.

DR. D'ESOPO: I don't think Carl really answered your question and, because it's so important, may I just add . . .

DR. MCDERMOTT: I wish you would.

DR. D'ESOPO: Your question was that at the end of the year, granted 100 patients, all of them with open cavities; all of them positive. You didn't ask what happened if you treated 100 patients now at the end of the year under those conditions. Our experience is that just about every one is positive. Now, if Carl would answer that question.

DR. MCDERMOTT: Unhealed lesions, Carl, tough TB.

DR. TEMPEL: Well, our cases are fairly tough. At eight months one-third of the cavities are still open. I don't think that's a very benign form of tuberculosis, although I must admit that in our group we do have very favorable cases to treat. To get to the next question, I would still say that in the combined intermittent regimen there would be a high conversion rate, and of those present I would say more than 50 per cent of them would be resistant; but they wouldn't all be resistant at that point.

DR. MCDERMOTT: I think this is a terribly important point and the reason I think it's

an important point is because, as editor of the official journal of the American Trudeau Society, I am in a sense a "Dr. Gallup" of the thinking in the field. Time after time I receive manuscripts, the opening sentence of which is "Now that PAS has done away with the problem of streptomycin resistance, we have done such and such." Dr. D'Esopo has said that in unhealed lesions, lesions which remain unhealed, that is definitely not the case. Dr. Tempel has made the very important point—and I think this point is crucial—that, when one is analyzing these phenomena, one is dealing with a very small minority of the patients with which one starts. Now, I would like to make the perfectly outrageous suggestion to the effect that I personally am unconvinced that PAS does anything very much about the emergence of streptomycin resistance; in fact, I suspect a great deal of the action of PAS takes place in the sputum bottle, where it has been shown by some workers at Ray Brook that very high concentrations of PAS are present. Ross, you mentioned that on PAS the percentage of conversions is higher. Has that been the universal experience?

DR. MCLEAN: I think you're referring to the isoniazid study.

DR. MCDERMOTT: No, you said anything with PAS in it.

DR. MCLEAN: Well, what I thought you meant was the delay in the emergence of resistance. I believe that PAS does delay the emergence of resistance on the basis of the information which is available to me through the Veterans' study. In order to point out the significance of your loaded question with respect to open cavities after one year of treatment, I think you can refer to the *Tenth Transactions* of the cooperative study and find there—I believe by our Captain Dye—a tabulation of cases which were positive after nine to twelve months of continuous chemotherapy on three streptomycin regimens: a gram daily, a half gram daily, and a gram twice a week. I believe you will find that, after nine to twelve months of continuous treatment with either one of those three combined streptomycin-PAS regimens, approximately 30 per cent are resistant to 10 micrograms of streptomycin per cc. of solid medium. The results are not broken down by cavity or no cavity.

DR. MCDERMOTT: But they were discharging bacilli?

DR. MCLEAN: They were all positive.

DR. MCDERMOTT: Guy, do you want to speak to that point?

DR. YOUMANS: The point here that's never been too clear to me is what is the mechanism whereby combined therapy apparently does reduce the emergence of resistance to streptomycin. Is it because PAS in this case actually inhibits the growth of the resistant cell or is this so-called effect a reflection of the greater therapeutic efficacy of the two regimens? From the discussion just preceding and the comments here, I might be inclined to think that it may be a reflection of the increased therapeutic efficacy of these combined drugs. I would appreciate some information on this myself.

DR. MCDERMOTT: Bill, do you want to speak to this point? Do you or do you not believe that PAS—we're not talking about whether PAS has an independent antituberculous action, although that will come in with it—but does it do something about prolonging the period during which streptomycin is active?

MR. STEENKEN: I really believe it does. I think it's the combination of the two drugs which has the ability to suppress emergence of the SM-resistant organisms; likewise, streptomycin has the same effect upon delaying the emergence of the PAS-resistant organisms. We have paid very little attention up to the present regarding PAS resistance and I think we should start to think more of it because we are seeing more, and there are articles to be published showing that patients on combined therapy also develop PAS resistance and do not respond as well. However, I'd like to bring out something else at this time, and that is that the body can handle resistant organisms as well as it can handle

sensitive organisms. When a lesion inspissates or a cavity closes, the sputum goes negative, so you have no organisms to test and don't know whether they are sensitive or resistant. And when those organisms are in a favorable environment, such as a caseous area, where no one speaks of organisms being dead, the resistant organisms can die off just the same as the sensitive organisms, so that, when we get the so-called target-point lesion, we do not know whether these organisms have gone through the resistant stage before they died.

DR. MCDERMOTT: The point having to do with PAS obviously is brought out because of the questions which have to do with the use of isoniazid and streptomycin together, or any other drug combination. I realize that the chairman is alone in his position, although I suspect a slightly kindred spirit on the part of Dr. Youmans. Actually, what I am trying to say is this: We all did a number of things at the same time. We stopped giving 3 grams of streptomycin and went to 1 gram, and then to 1 gram twice a week. Many of the series were done with reasonably favorable lesions in which there is a very high percentage of conversions, as Dr. Tempel has brought out. Finally, we have administered a drug, PAS, which I believe makes the culture of tubercle bacilli from the sputum bottle a very difficult proposition. In addition to that, Bill Steenken has made a terribly important point, namely PAS resistance. And I'm just saying that, if you should view all the statistical data and assume that whether or not one gets a positive sputum depends on whether the organisms in the bottle are PAS susceptible or PAS resistant, you might come up with some entertaining ideas on the subject of how the administration of PAS affects streptomycin. Now, the reason the question is important is how long is streptomycin-PAS good in an individual patient. In very general terms, I take it, Ross, you think that in about 70 per cent of the time it would be good for a year. Is that right?

DR. MCLEAN: If their cultures remain positive for that length of time and without specifying whether there are large or open cavities or not. I certainly agree with the general clinical observation that persistent open cavities consistently discharge bacilli. You will almost surely have most of them, if not all of them, resistant, in all probability by the end of the year. It does not necessarily mean that they will be deteriorated clinically, though they probably will be failing to improve further.

DR. MCDERMOTT: Well, now, can we estimate how long in the average patient—in the mythical average patient—how long can one anticipate drug activity from strep-PAS? Over how many weeks or months? Nick, do you want to take a shot at that?

DR. D'ESOPO: Drug activity is the cue phrase there.

DR. MCDERMOTT: Well, effectiveness.

DR. D'ESOPO: I can summarize it somewhat in this way. If cavities do not close by six months, it's unlikely that they will close; and thereafter it becomes likely that the organisms have become resistant to streptomycin.

DR. MCDERMOTT: Do you still give PAS thereafter?

DR. D'ESOPO: No, I don't. And may I go back a moment and answer one of your comments about the possibility that PAS in the bottle gives you a high percentage of negative cultures. I don't think that's right because we treated a great number of patients who were streptomycin resistant—of course, PAS sensitive; that is, people who got streptomycin before we had PAS and then we re-treated them with streptomycin-PAS. It's not difficult at all to get positive cultures on those people. It's true that PAS is in the bottle, but it doesn't prevent our growing them out.

DR. MCDERMOTT: Carl?

DR. TEMPEL: If we continue the use of streptomycin and PAS for eight to twelve months, we know that it remains effective. I think that was one aspect of this question which Walsh asked. We know that, if we stopped that drug combination, at least 20 per cent of those patients would relapse. Now, that means it is still being very effective, so

that in continued long-term therapy it is extremely rare to see a relapse while the patient is on the drug. Now that's not the case when you use streptomycin alone or INH alone. We have many relapses in the INH group after the fourth or fifth month when the incidence of resistance is high, and we attribute that relapse largely to that; so that, in effect, is one of the answers to the problem which will come up a little later, that the resistant organism is not innocuous because it causes progressive disease after resistance develops.

DR. MCDERMOTT: Well, Carl, do I gather that your position is that on streptomycin-PAS, when strep is given intermittently—by that I mean twice a week—relapse under such therapy within a period of one year is quite a rare phenomenon?

DR. TEMPEL: It's very rare.

DR. MCDERMOTT: Is there general agreement among the panel that that would hold for, let us say, acute caseous pneumonia? Nick?

DR. D'ESOPO: Yes. I think that relapse is rare if the regimen is uninterrupted.

DR. MCDERMOTT: John, have you an opinion on that point? Ross?

DR. MCLEAN: To the best of my knowledge, in original treatment cases, uninterrupted, it is quite uncommon.

MR. STEENKEN: Is this on strep-PAS that you are talking about?

DR. MCDERMOTT: That's right—on strep-PAS. As a matter of fact, it's my understanding that in the USPHS forty-week statistics, relapse was virtually identical on all three regimens and ran around 6 to 7 per cent. Is that what the relapse rate is with the Veterans?

DR. MCLEAN: Our relapse with streptomycin-PAS at most points up to a year is down around 1 per cent or less, and not over 2 per cent; somewhat higher with the other regimens, some of those above 5 or 6 per cent.

DR. MCDERMOTT: This is relapse under therapy?

DR. MCLEAN: Relapse during therapy—continuous therapy. They're not all previously untreated cases, however, but they're all streptomycin-sensitive cases.

DR. MCDERMOTT: Well, again I find myself at variance with the members of the panel. All I've got to say is that, when any new drug is introduced, such as viomycin or other drugs, one has a conference in which an awful lot of patients are presented who seem not to have done so remarkably well on strep-PAS. Perhaps that is not an entirely fair comment and I realize its unfairness.

Well, then, it is believed that, in terms of a year, strep-PAS seldom yields relapses under therapy. Ross says that's true and Nick says that's true on uninterrupted therapy. Carl makes the point that, even on intermittent therapy, that's also true. Isn't that so, Nick?

DR. D'ESOPO: Yes. I'd like to say something that might explain the cases you see at conference. Very often you hear from the history that the patient got chemotherapy for a year. You say "Was it uninterrupted?" and the man says "Yes," and then you ask the patient or look at the nurse's notes and go into great detail, and you find that the regimen has not been continuous. The patient has had some difficulty with PAS and it was discontinued and streptomycin was continued; the patient has had a lot of diarrhea and vomiting, and things like that. You find that the patient isn't really a "streptomycin original" patient; he had a little bit of therapy in 1947 and, in most cases where I have been surprised at relapses on uninterrupted therapy, I've been able to find something wrong. The regimen has not really been ideal.

DR. MCDERMOTT: But Carl says that on intermittent therapy the same thing holds.

Well, Nick, I think your comments here are very much to the point; could I ask you a question again? That is, how do you think, if it is the consensus of the panel (the chair-

man dissenting) that streptomycin-PAS over a period of a year has a very low relapse rate under therapy, how do you think isoniazid looks in that same situation over a year?

DR. D'ESOPO: I have no personal experience with a year of strep and INH.

DR. MCDERMOTT: How about isoniazid alone?

DR. D'ESOPO: Well, they do relapse,—yes, they relapse.

DR. MCDERMOTT: They relapse? Ross?

DR. MCLEAN: The accumulated statistics in the form of a summary report, as they now stand, indicate that the bacteriologic relapse from isoniazid alone is certainly, in our experience, greater.

DR. MCDERMOTT: Will you define bacteriologic relapse, Ross?

DR. MCLEAN: These are individuals who have had consistently negative cultures who have reverted to positive cultures.

DR. MCDERMOTT: And that is relapse?

DR. MCLEAN: Yes; that's what we call a bacteriologic relapse. It does not imply clinical deterioration necessarily. Combinations of isoniazid with either streptomycin or PAS do not extend to a year of continuous uninterrupted therapy. Some of the patients who receive isoniazid alone do and the relapse rate rises to the level of approximately 10 per cent toward the end of the year, or slightly more; that is bacteriologic relapse.

DR. MCDERMOTT: Ross, if I could shoot a loaded question—if this doesn't imply clinical deterioration, why do you use it?

DR. MCLEAN: Well, it expresses in my mind the fact that you had once achieved sufficient bacteriostasis to cut the number of bacilli being discharged in sputum down to such a small number that you are unable to recover them on culture. Now, when they become positive again, it implies to me that you are discharging more bacilli and that, in that sense, you have lost to some degree the degree of tuberculostasis which you had once achieved.

DR. MCDERMOTT: In other words, you are assuming that the sputum is an aliquot of the lesion—of the principal lesion?

DR. MCLEAN: Well, not necessarily; I'm assuming that from somewhere you're getting more organisms being discharged than you were before.

DR. MCDERMOTT: Carl, will you speak to that point?

DR. TEMPEL: You ask about deterioration on an INH therapy?

DR. MCDERMOTT: That's right.

DR. TEMPEL: Most of our cases were on combined therapy, so our experience was limited to 59 patients whom we followed from four to eight months. Of those who were negative, or those who had positive cultures with sensitive organisms, there was deterioration in only one of ten, about a 10 per cent rate; but in those in whom we found the cultures positive and resistance developed, 50 per cent showed deterioration. To us, at least, it means that long-term isoniazid therapy in this group of patients whom we treated was not successful and we wouldn't advocate its use alone.

DR. MCDERMOTT: Guy, do you have anything to say on that point—that Ross and Carl were talking about, bacteriologic relapse?

DR. YOUMANS: Well, there really isn't very much new I can say except, possibly, in relation to isoniazid. It is the experience that bacteriologic relapse does occur and, from what I have seen of published material and have heard, I have every confidence that in a lot of these cases, at least, bacteria which do reappear in the sputum are still virulent or may be still virulent.

DR. MCDERMOTT: Bill, do you want to speak to that point—about bacteriologic relapse?

MR. STEENKEN: Well, I may be stealing some of the fire from Dr. Middlebrook's

panel if I start to become involved in the bacteriology and the change of virulence of tubercle bacilli from patients while under isoniazid or any other . . .

DR. MCDERMOTT: Bill, hold yourself back about 50 per cent, and really let go.

MR. STEENKEN: I know what Walsh is driving at. He's trying to get a little scrap started because many of the clinicians I know say they do not see the same type of relapse in patients while under isoniazid therapy as they've seen with streptomycin. In other words, when the organisms became resistant to streptomycin, you could always see the X-ray relapse and the symptomatic relapse of the patient. However, it's generally known today that, even with the development of isoniazid resistance, you do not see this X-ray relapse and many times you do not see any clinical relapse. We have found that some of these patients are putting out organisms which are resistant to isoniazid and have very little virulence for guinea pigs. Don't ask me what degree of isoniazid resistance; don't ask me too many details about it. We are still studying it and many of these strains do not produce disease in guinea pigs, although they are still viable on culture media. So, it introduces something for us all to think about. Much more work must be done. The U. S. Public Health Service is now running control studies and we are studying the phenomenon in our own laboratory. We are going to inoculate cultures of tubercle bacilli from patients before they go on therapy, regardless of the type of regimen they go on, whether with streptomycin and PAS or with a combination of three drugs or on one drug alone, and study the virulence of these organisms during therapy. Then we can see what happens to the virulence of the organism after the patient is removed from therapy. Then we are going to send these results to Washington and let the Washington office correlate these findings with X-ray and clinical relapse.

DR. YOUMANS: I'd just like to ask Bill whether he thinks that all or the majority of isoniazid-resistant tubercle bacilli are avirulent.

MR. STEENKEN: I cannot answer that question.

DR. MCDERMOTT: Bill, you made an assertion that clinicians say that there is not a correlation; that patients continue to improve despite the fact that they are excreting tubercle bacilli which are apparently resistant to isoniazid in the test tube. You believe that assertion—is that correct?

MR. STEENKEN: I didn't say they improve; I said they show no X-ray or bacteriologic or symptomatic relapse.

DR. MCDERMOTT: How do you feel about that, Nick?

DR. D'ESOPO: I think that when you treat patients with isoniazid alone there is a drop in the number of organisms on culture characteristically, and after the organisms become resistant to isoniazid there is a rise in the number of organisms on culture. Most often, the rise in the number of organisms on culture is not accompanied by either symptomatic or roentgenographic relapse. I think we have got to subdivide what we call bacteriologic relapse. In some cases with streptomycin-PAS, for example, postoperatively we've had one positive culture with one or two colonies on it, and then nothing further. Now, if you want to call that a bacteriologic relapse, you must categorize the phenomenon. You have other patients who have positive culture with one colony, but the next culture shows more colonies, and so forth, until you get confluent growth. I think bacteriologic relapse has to be quantitated.

DR. MCDERMOTT: Then, if I could just poll the members of the panel. Ross, is it your current belief that isoniazid alone is not maintaining antituberculous effectiveness for so long a period—we're talking now about the average—as strep-PAS?

DR. MCLEAN: Yes; I do not believe that for periods of treatment up to ten to fourteen months isoniazid is as effective as combined streptomycin-PAS.

DR. MCDERMOTT: John, do you have an opinion on that? Carl?

DR. TEMPEL: I don't think isoniazid alone is as good as SM-PAS, definitely not.

MR. STEENKEN: My opinion would be according to the type of case. If it was a miliary or an acute pneumonic type, it may be from what I see in rabbit work. But, in the caseous or cavitary type of tuberculosis, I don't know.

DR. MCDERMOTT: Nick, do you want to answer that question? Perhaps you had better.

DR. D'ESOPO: I believe it depends on the criteria set forth. As far as X-ray improvement is concerned, which I think is a very initial primitive sort of assessment, it probably looks as good. In terms of cavity closure, I don't know; in terms of the viability of organisms in resected lesions, I don't know.

DR. MCDERMOTT: John, have you opinions on that?

DR. JONES: Well, we haven't operated on any patients on isoniazid alone. We have still stuck to PAS and streptomycin—with isoniazid added. In those patients with streptomycin resistance we still give streptomycin-PAS and add the isoniazid to it. So I can't tell you anything about isoniazid alone.

DR. MCDERMOTT: Well, then, I think it can be summed up at this point to say that the panel, but not the chairman, believes that over a period of months streptomycin-PAS continues to exert antituberculous activity—we're talking of the average hypothetical case—whereas isoniazid does not exert such activity, or rather does not exert it for so long a period of time. Is that fair, gentlemen?

DR. MCLEAN: I'd like to just mention that, aside from duration of effectiveness, the relative proportion of cases which respond favorably to isoniazid—say the percentage which would show moderate or more X-ray improvement or the percentage which achieve negative cultures at various points in time of their treatment—is lower on isoniazid alone than it is on streptomycin-PAS in our studies.

DR. MCDERMOTT: In the VA studies? That is not the case in the USPHS studies, as I understand it. The USPHS studies assess strep-PAS, on the one hand, and isoniazid alone, on the other hand, as about the same. Right around 51 to 52 per cent have moderate or marked X-ray improvement on either regimen, whereas strep-isoniazid runs around 58 per cent. So that it all depends upon which series you read.

DR. MCLEAN: Well, I was referring to isoniazid alone. Statistical significance of any differences between combinations of isoniazid and streptomycin-PAS, and of streptomycin-PAS are not present in the Veterans' study at the present time, although streptomycin-PAS does seem to have an edge on the others. There are background factors which may explain that, and I don't think that there's a serious discrepancy between these studies at all.

Dr. MCDERMOTT: Could we define these relapses which occur on isoniazid alone a little more precisely; that is, exclusive of bacteriologic relapse, Ross, what kind of relapse was seen?

DR. MCLEAN: I think the type of relapse in addition to bacteriologic relapse which is most frequently seen, or as reported to us, will be an extension of the infiltrative component on the X-ray or, more commonly, an increase in the size of cavity.

DR. MCDERMOTT: More commonly an increase in the size of the cavity?

DR. MCLEAN: Usually following an earlier decrease in the size of cavity.

DR. MCDERMOTT: In other words, changes in cavity size?

DR. MCLEAN: Yes.

DR. MCDERMOTT: How about new areas of disease, totally new areas of disease?

DR. MCLEAN: Well, these do occur, but I couldn't exactly tell you in exactly what proportion of cases.

DR. MCDERMOTT: Carl, will you speak to that point?

DR. TEMPEL: New areas of disease is what I've referred to before as relapse.

DR. MCDERMOTT: You were referring only to new areas of disease, not changes in cavity size. Nick?

DR. D'ESOPO: Well, the most common unfavorable change is an increase in the number of organisms on culture, the second is an increase in cavity size, and the third is new lesions.

DR. MCDERMOTT: Would you give us a rough breakdown in their order of occurrence?

DR. D'ESOPO: The increase in number of organisms on culture is, avoiding percentages, very common; increase in cavity size is moderately common—let us say, occurs in many cases—and new lesions, I think, are unusual.

DR. MCDERMOTT: New lesions are unusual. You would also say they were quite unusual with streptomycin-PAS?

DR. D'ESOPO. They're rare. They don't occur.

DR. MCDERMOTT: They don't occur. The Chair is amazed at the strides which have been taken in the treatment of tuberculosis in the last ten years. We're now down to the point of how many tubercle bacilli the patients put out per month. In all seriousness, I must express my personal opinion that bacteriologic studies of sputums are not necessarily representative of what is going on in the host-parasite relationship within that patient.

Now, how do we feel about streptomycin and isoniazid together? It is agreed by the panel that combined therapy is proper; it is agreed that isoniazid has some activity and that strep-PAS is better. How do the opinions run on the use of streptomycin-isoniazid? Carl?

DR. TEMPEL: I think at this stage of investigation in our studies of about eight months, when there were enough cases to evaluate and compare with SM-PAS, we must, in all fairness, say that both regimens appear to be about equal. In our series, however, we had about 146 on strep-PAS and 109 on strep-INH, and comparison of these two resulted slightly in favor of the strep-INH. There were more moderately advanced and far advanced lesions in the other group, so there appeared to be advantages in favor of strep-INH. In both regimens in this comparative study we made and reported yesterday, the results were quite good. In other words, when you have a sputum conversion rate of 80 to 90 per cent throughout the period and less than 10 per cent of the group, even when you get up to eight to ten months, are resistant (more than half of those being sensitive), that's really achieving good effective chemotherapy over long periods of time. But I believe that, at this stage of comparison, I would rate them about the same in effectiveness with a slight edge for the strep-INH. When you compare all of these five factors, that is, patient acceptance over prolonged periods and ease of administration, and so forth, I think there's a clear-cut advantage in favor of strep-INH. Everything considered, I believe at this stage (eight months at least) I would favor the use of the strep-INH regimen for routine use.

MR. STEENKEN: Walsh, could I ask the clinicians on the panel a question?

DR. MCDERMOTT: Sure.

MR. STEENKEN: Given a patient with pulmonary tuberculosis, what regimen would the clinicians use in treating him with the accepted therapies that have been evaluated today?

DR. MCDERMOTT: Why, I think that's an excellent idea, Bill. How do you feel about it, Ross?

DR. MCLEAN: I'd start off with streptomycin-PAS.

DR. MCDERMOTT: Carl? I'm skipping you, Guy.

DR. TEMPEL: Well, if I had an early case in which I felt success could be predicted in eight to twelve months, I'd use strep-INH. I've already explained I can only compare them at eight months. If I had a tough case and the patient was going to require drug therapy for one to two years I would give him strep-PAS—that's the only regimen I have had experience with for one or two years. But I believe it won't be long before we can use the strep-INH because we'll have experience with that period. Personally, I think for any cases that respond promptly the best regimen at this time is strep-INH.

DR. MCDERMOTT: Nick?

DR. D'ESOPO: Well I'd use streptomycin-PAS because I have most experience with it and because it's been used for a longer period of time; but I'm—May I go on just a moment—I think the kinds of comparison are important. I think there may be two regimens which will give equal results as far as X-ray change is concerned, even though one may be greatly inferior to the other. The second important criterion is the sputum. I think two regimens may given the same conversion rates, even though one is inferior to the other. And the third criterion is the ability of the regimen to close cavities. When you get to cavity closure you've really found something important. I think when two regimens close cavities equally well, you can begin to say that they are equally effective. The fourth criterion is the viability of organisms in closed lesions. See how the two regimens compare there. Finally, the relapse rate when the patients are off therapy. I just want to emphasize that the comparison of X-rays to decide whether X-ray shows moderate or marked improvement is not a good evaluation of two regimens.

DR. MCDERMOTT: You believe there are some five or six categories and among them you would use cavity closure as an indication of antimicrobial effectiveness. Is that correct?

DR. D'ESOPO: When you get to cavity closure; when two regimens look equally good as far as cavity closure is concerned, then I think you can begin to think that they really might be equally good.

DR. MCDERMOTT: John, you probably have more cavities in your hands than the rest of us have. Could you give us your notions on cavity closure in so far as drug activity goes?

DR. JONES: Personally, I think if I were going to evaluate a patient, I'd start him off with PAS and streptomycin and re-evaluate him in four months; then I would decide whether or not this patient was doing well enough on that so that I could proceed with surgery in the next four months or go on with INH and then re-evaluate the patient at the end of six months, that is, two months later. I don't think that I would be willing to go along on just INH alone. I would start off routinely on PAS and streptomycin and then, I think, I would make a decision at the end of four or six months with the idea of proceeding with surgery to eradicate that cavity about the time this patient is going to give resistance to streptomycin, or before that time.

DR. MCDERMOTT: You do agree it does happen then?

DR. JONES: Yes.

DR. MCDERMOTT: John, how do you feel about giving streptomycin and isoniazid together at the beginning—before surgery?

DR. JONES: Well, I think in a lot of cases we have to give all three drugs because there's a demand for it. Personally, I would just as soon go on streptomycin-PAS and reserve the INH.

DR. MCDERMOTT: For postoperative use?

DR. JONES: No; until the fourth or the sixth month before surgery and then make a

decision at that time whether it is necessary to give it and, if you still have a cavity on your hands, then I think I would give INH for a couple of months before the surgery; then you'd still have streptomycin-INH to use after the surgery.

DR. MCDERMOTT: Nick has expressed the opinion, John, that cavity closure can be used as a measure of antimicrobial effectiveness. We're not talking about clearing of the noncavernous portion now but cavity closures. Have you opinions on that?

DR. JONES: Well, I'm always suspicious of a closed cavity so I think I'd go ahead and resect it anyway.

DR. MCDERMOTT: Nick, do you want to speak to that point again?

DR. D'ESOPO: Well, I wasn't talking about the practical aspects of it. I was talking about cavity closure as a measurement of a regimen.

DR. MCDERMOTT: Bill?

MR. STEENKEN: Don't you think that cavity closure is just a gross tool of measurement? In other words, cavity closure is just showing what you're doing to the tubercle bacillus; if you're affecting the tubercle bacillus, you're therefore affecting the pathology which the tubercle bacillus causes. But I'd like to ask a question here. They seem to be talking quite loosely here of PAS and strep, and what not, but they go past it; they say they give it every day, but they don't mention how much they give each day, so I think everybody in the audience is at a loss. I'm sure when you start to ask each one of them, they're all using a different regimen.

DR. MCDERMOTT: Why, Bill, we can't go on to dosage until we can agree on drugs. We haven't done that thus far. As I understand it, one-half the panel would give strep-PAS and one group—at least Carl—would give strep-isoniazid, and John Jones would give strep-PAS and follow it with isoniazid. Is that a fair reporting of what's gone on? I can express an opinion on cavity closure. I just don't see how that can be used as a measure of antimicrobial effectiveness. That is, it seems to me that there are too many other factors which come into the question of cavity closures.

DR. D'ESOPO: If you take patients and randomize them, give one patient one regimen and one, another, and do not introduce mechanical measures such as collapse therapy or resection and if the cases stack up differently in terms of cavity closure, I think that would be quite significant because you must recognize that the cavity is really an open necrotic lesion. We're not very worried about closed necrotic lesions but the cavity had best be looked upon as an open necrotic lesion, and I think the case is not controlled unless the cavity is closed. Chemotherapy does close cavities.

DR. MCDERMOTT: Carl?

DR. TEMPEL: When we used single agents at four months, cavity closures did not exceed 4 or 5 to 10 per cent. With our combined regimens—the two regimens of choice which we've already mentioned—it runs from 20 to 30 per cent at four months; and at six months it's 30 to 40 per cent. When you reach eight months, it's 60 to 70 per cent. That shows progressive effectiveness of the drug to produce cavity closures. In similar cases treated on one drug alone, the rate of cavity closure is not nearly that high. I am sure it was nowhere near so high when we had no drug therapy at all. So I think that it is a useful way to compare agents. These rough measures Nick mentioned, the resolution of the tuberculous infiltration, for example, he says are not such useful guides. As we get into our effective agents, that is true but those were useful tools when we compared amithiozone, Diazone, terramycin, viomycin, and many other drugs that we were studying, so that, as a preliminary pilot study, those are very useful guides for comparison. I think they're of real value but, as he mentioned, as we get into the effective regimens in which the improvement reaches 70 to 75 per cent at eight months, we can use criteria such as cavity closure.

DR. D'ESOPO: I didn't mean to minimize the degree of X-ray change. In the earlier studies when you saw a marked degree of X-ray change, I think it answered the question. There was some effect and that was all you could say.

DR. MCDERMOTT: I think we will all agree that our methods of estimating what is going on are very crude indeed. Bill Steenken has put his finger on an important point when he says that when you affect the bacillus you undoubtedly affect the lesion which is caused by the bacillus. Nevertheless, I happen to believe that the factors which affect the cavity are very complicated indeed. A cavity is everything from a little thin circle to an area of nothingness in a large caseous lobe and, if we are going to use the word cavity as a biologic entity by which we will measure antimicrobial activity and decide between drugs, I just don't see it.

Now, Carl, you've had some experience with miliary TB, haven't you, there at Fitzsimons? What's been your experience with miliary and isoniazid?

DR. TEMPEL: Our only experience has been with the 14 cases of miliary and meningitis in which we used all three drugs. You might say that those 14 have shown a most favorable response.

DR. MCDERMOTT: Carl, have you ever seen a meningitis develop in a patient with miliary TB on isoniazid who had had no meningitis when therapy was started?

DR. TEMPEL: That was quite common when we used streptomycin alone, but I have no figures to cite. It is certainly quite rare now that we use combinations of drugs.

DR. MCDERMOTT: I think that Dr. Riley and Dr. Harrington found a high incidence with strep-PAS—you mentioned streptomycin alone—that is, approximately a third of the patients with miliary tuberculosis developed meningitis on strep-PAS. You say that is now rare. Have you seen it on isoniazid at all?

DR. TEMPEL: No.

DR. MCDERMOTT: Has any member of the panel seen any cases of meningitis develop while under isoniazid therapy? Nick, do you wish to speak to that? Ross?

DR. MCLEAN: I have no personal experience. We have one case which is subject to more investigation as to details.

DR. MCDERMOTT: I can mention that in our own experience, Dr. Muschenheim and I have seen no such cases and this includes 3 patients who had tubercle bacilli in the cerebrospinal fluid at the time isoniazid was started. Recently I had a chance to talk to Dr. Honor Smith and she has seen no such cases. I mention this fact chiefly to indicate a way to measure the effectiveness of drug therapy which has not previously been mentioned. Now, what about the toxicity of isoniazid? Carl, you indicated you wanted to talk about that.

DR. TEMPEL: I merely want to add one thing. At the last Army-Navy-VA conference, this one drug appeared to be the least toxic of those used singly. Only about one per cent have to discontinue this drug. With strep-PAS it is at least 5 per cent, so we can say that, of the three best drugs, isoniazid is the least toxic. When there is toxicity, however, the results seem to be quite serious. Two of our patients had convulsive seizures, one developed a psychotic episode, several had febrile episodes which really would not permit us to resume use of the drug. However, in a disease as protean in its manifestations as tuberculosis, and the chronic course of the disease, you have a usefulness for some of these other drugs, even though they have limitations mostly of a toxic nature. I know that we have used terramycin in patients who cannot take PAS. Viomycin, we have frequently substituted intermittently in resistant streptomycin cases and those developing serious reactions to streptomycin. There are these drug toxicities and serious reactions in patients which require drug substitution so we should hang on to any agent that is effective and can so be used.

DR. MCDERMOTT: Carl, would it be a fair summary of your position, then, that streptomycin, isoniazid, and PAS have widespread usefulness; that viomycin and terramycin have usefulness but that it is restricted to highly specialized situations? Are there any other antituberculous drugs which are worthy of comment? You have had no experience with pyrazinamide? What was your opinion on the Yeager studies on pyrazinamide? Did you have a chance to go over them?

DR. TEMPEL: I think the report was favorable in that the drug had usefulness for short periods, and I think for that reason it may yet have a place in such acute emergencies in which usefulness of a drug for three or four weeks or a couple of months would be important.

DR. MCDERMOTT: Ross, do you care to comment on Carl's comments? It was a beautiful summation, I think.

DR. MCLEAN: I think there is nothing to add to it except that those hospitals in the Veterans Administration-Army-Navy Cooperative Study who have studied Aldinamide have confirmed the short-term effectiveness of this drug, particularly symptomatically, but the problem of bacteriology is not very well elucidated.

DR. MCDERMOTT: Bill Steenken, do you have any comments on any other antituberculous drugs?

MR. STEENKEN: I don't, but I want to bring out that in acute miliary tuberculosis in rabbits, PAS and pyrazinamide are poor antituberculous agents in relation to INH and strep.

DR. MCDERMOTT: Do they have any activity at all?

MR. STEENKEN: Yes, but they are very limited. They prolong life.

DR. MCDERMOTT: John, have you had any experience with pyrazinamide? Nick? Do you have a comment you wish to make?

DR. D'ESOPO: I agree with Carl. I would simply like to emphasize the usefulness of terramycin occasionally. Sometimes you get a patient who is resistant to PAS and INH but, for some reason or other, has never received streptomycin and I think it is extremely useful to remember that streptomycin and terramycin can act like streptomycin and PAS.

DR. MCDERMOTT: That streptomycin and terramycin can act like streptomycin and PAS?

DR. D'ESOPO: Yes.

DR. MCDERMOTT: Well, at the beginning of this panel session, the chairman told the participants in the panel that he was going to use shock tactics on them and that what we wanted on the panel today were men with strong opinions. I have attempted by shock tactics to extract from the panel members their opinions on these various subjects. I think the record is pretty clear and I would like therefore at this point to throw the questions open to the members of the audience. If they will please address their questions to a particular member of the panel, it will keep traffic fairly well in line. Are there questions?

DR. EMIL BOGEN: First I'd like to ask the panel members why they are so afraid to use the three drugs at the beginning without waiting until resistance develops to one?

DR. MCDERMOTT: All right. Ross?

DR. MCLEAN: Who said we're afraid? I doubt if anybody here is, but...

DR. MCDERMOTT: I am.

MR. STEENKEN: I am.

DR. MCLEAN: O. K. I'll simply start off by saying that, in a cooperative study for a proper adequate evaluation of what you are dealing with in highly potent antituberculous

drugs, in using all three drugs we may not demonstrate anything very sharply or clearly. Therefore, for the immediate future it will be best to restrict the use of such drugs to desperate situations or very clearly and carefully delineated cases from which one may hope to draw some conclusions with respect to inter-regimen comparisons.

DR. TEMPEL: I mentioned the 14 cases of meningitis in which we used the three drugs, and we were very much impressed with their usefulness. We have 44 pulmonary cases on it, but since they have only gone a few months I don't think its fair to come before a group like this and assess any value at that point. I should say we are not afraid to use it in that many people. But if we come back next year, all these folks who have used the three drugs together will be in a position to say if it was the best way to do it, and I think that is the crux of the situation of the panel. We have not gone long enough to express an honest opinion about it.

DR. MCDERMOTT: I'm going to express an opinion on that point, and that is that I believe very strongly that it is a mistake to use streptomycin and isoniazid together except in very serious and immediately threatening situations. I believe that because it seems to me that isoniazid and streptomycin are the two major antituberculous drugs. We are dealing with a chronic disease. I hope that our patients always do as well as the members of the panel have indicated that they do over a one-year period, but I think we will all agree that there are some who are in difficulties in their second, third, fourth, and other years. In such circumstances it seems to me to be very important not to sacrifice the possible usefulness of a major antituberculous drug for a mere bacteriologic result in the first three or four months of the treatment of so chronic a disease. Now I would be the first to state that I believe that the relation of the isolation of isoniazid-resistant bacilli from a patient to whether or not isoniazid is effective in that patient is a subject which is so confused as to have little meaning. Certainly, from the standpoint of over-all clinical effectiveness, as members of the panel have indicated, such drug resistance tests are not necessarily pertinent. Nevertheless, there is presumably a hard core of patients who have isoniazid-resistant infections in the same way that patients have streptomycin-resistant infections; I believe the experience has been that on streptomycin-isoniazid in large proportions one of two things happens along about the sixth or seventh month; either one can no longer cultivate tubercle bacilli from the patient's sputum or the bacilli are resistant to both drugs. So it is for that reason I feel it is a mistake to give the two together. Obviously, here again, I do not have the concurrence of the panel.

MR. STEENKEN: Walsh, could I say something? I agree with what you said 100 per cent. On no one regimen is the result predictable. We all know the effects of pneumonectomy and surgical procedures before the advent of chemotherapy. Many of the surgeons were ready to throw up their hands on removing a lobe. Therefore, if you give all your drugs at one time and they are a failure, that patient loses drug coverage during the surgery, and surgeons do not like to operate without drug coverage. The next thing I would like to bring out is that the more drugs that are being used the more patients are going to be treated on a nonhospitalized basis, and the more people are going to become infected with resistant organisms. And this is not going to be a single resistance but multiple resistance. The time is coming when the physician is going to have to depend on the laboratory to a much greater extent because, when a patient comes in with any tuberculosis, unless you know the resistance of those organisms, you cannot use any regimen of drugs sensibly.

DR. MCDERMOTT: Last year, when Bill Tucker was chairman of this panel, Dr. Waring asked a very penetrating question. I'm sure you remember the question. It was: what should you do with a child that you knew was not a cutaneous reactor to tuberculin who

had become a cutaneous reactor to tuberculin under your observation? Now you've had a whole year to reflect on that, Bill Tucker. No matter how much you are hiding down there, could you give us your opinion?

DR. TUCKER: In concurrence with your panel, Dr. McDermott, I would treat that child with drug therapy.

DR. MCDERMOTT: You would treat it. How long would you treat, Bill?

DR. TUCKER: Six to eight months.

DR. MCDERMOTT: How do you feel about that, Paul Bunn?

DR. BUNN: I'm flabbergasted.

Question from floor: Would the age of the child make any difference?

DR. MCDERMOTT: Would it, Bill?

DR. TUCKER: Yes.

DR. MCDERMOTT: How much?

DR. TUCKER: I think all figures show that the greatest hazard is during the first two years of life, decreasing up to the fourteenth or fifteenth year with an increase after that. So I think the greatest danger would be in the first year or so of life, also in the adolescent period.

DR. MCDERMOTT: How about a nurse, twenty-two years old? Well let's pick on somebody else, Carl Muschenheim. Carl Muschenheim, how would you feel about a twenty-two-year-old nurse who had recently become a tuberculin reactor?

DR. MUSCHENHEIM: I would treat her. Not with three drugs, but with one drug, just as Bill said.

DR. MCDERMOTT: Bill, which drug?

DR. TUCKER: Carl is the one who is going to treat her.

DR. MCDERMOTT: Doesn't matter, this is an open meeting. Paul, you said you were flabbergasted. Would you like to elaborate on that?

DR. BUNN: I would like to emphasize what Bill Tucker said. In the first year of life the child probably deserves therapy, but after the second year it should depend on the appearance of clinical disease. There is no reason to waste good drug with the associated toxicity on the kind of disease which is tuberculin positive only.

DR. MCDERMOTT: I want to ask Guy Youmans what he thinks the chances of the emergence of drug-resistant organisms would be in such a situation?

DR. YOUMANS: I'm afraid anything I say would be merely a guess. But on the whole, if the therapy in such conditions were effective, I think the chances for the emergence of resistance would be very slight.

DR. MCDERMOTT: Bill, how do you feel about it?

MR. STEENKEN: I'd say the chances of emergence of resistant organisms under combined therapy would be nil. However, we do not have agents we are certain will sterilize the host of his infecting organisms.

DR. MCDERMOTT: You've changed since yesterday.

MR. STEENKEN: In a certain type of lesion, I said. There may be a difference between a caseating and a noncaseating lesion. We do see relapses in animals that have caseation.

DR. YOUMANS: Just one further comment. I'm a bacteriologist and not a chest physician. I have frequently wondered why, apart from considerations of toxicity, was there such reluctance to treat early minimal tuberculosis and even, as in this case, to treat a positive tuberculin test. It is granted, I think, that drug toxicity is the major item involved. Aside from that, especially with bacteriological evidence we have now indicating the possibility of the bacteriocidal activity of some drugs, particularly isoniazid and possibly streptomycin, it makes good sense to me, especially if the drugs don't do the patient any harm from the toxic effects per se. That is, why the reluctance if it's not toxicity?

DR. MCDERMOTT: Nick, would you distinguish between a minimal lesion and the situation in the child we have been discussing in terms of the emergence of drug-resistant organisms?

DR. D'ESOPO: Well, I think it is very difficult to know what lesions you are dealing with in a child. We really don't know if streptomycin gets into certain closed lesions. If the child has a non-sloughing lesion, then we are not so sure the drugs get in such lesions.

DR. MCDERMOTT: No, I meant the adult with the minimal lesion, on the one hand, and an adult, if you will, who is a recent tuberculin converter but has no lesion that you can demonstrate. Would you distinguish between those two patients in terms of the emergence of resistance of drug-resistant organisms; or would you regard them as both equally at risk?

DR. D'ESOPO: Oh, I don't think anybody knows the answers to those questions. In both cases I think the lesions are closed. That is, that we have negative cultures. And it raises the general question, is there any difference in drug resistance in closed and open lesions. By open lesions I mean lesions that are sloughing. The organisms are actively growing in sloughing material. On the other hand, you have closed lesions where the organisms are alive but in non-sloughing lesions. If we knew the answer to that question, I think I could answer you.

DR. MCDERMOTT: Well, your modesty is commendable, Nick, but as we stated, this is a forum for opinion. Facts are for papers, but panels are for opinions. And whether we like it or not, this is a very practical matter. People do have twenty-two-year-old nurses on their services who have become tuberculin positive.

DR. D'ESOPO: That's different—if you just want opinion.

DR. MCDERMOTT: That's all we've wanted all day.

DR. D'ESOPO: I wouldn't treat the nurse who is a recent converter. She has tuberculous infection and I would look for evidences of progressive tuberculosis which your minimal lesion is. As far as the child is concerned, I think I'd call Edith Lincoln on the phone—and I think she's in the audience, by the way.

DR. MCDERMOTT: I think she was here at first, but I haven't seen her lately. Oh, Edith, I've been looking all over for you. How do you feel on that point?

DR. LINCOLN: I wouldn't make up my mind to treat him merely on account of his age. I'd look for evidence of lesions in the mediastinum and I'd watch the spinal fluid. Even then, we have no evidence that streptomycin does any good in a progressive primary lesion. The treatment of progressive primary lesions has been associated with an incidence of meningitis. On the other hand, we have not seen the development of meningitis in these cases treated with isoniazid.

DR. MCDERMOTT: You would not favor treating on the basis of age alone, or on change in cutaneous hypersensitivity to tuberculin alone, but you would favor treating if you could find definite evidence of a primary complex, a recent one.

DR. LINCOLN: I would treat with chemotherapy only if I were convinced that chemotherapy was going to prevent meningitis. Because we know that it will not prevent other complications. We know that it will not cure primary tuberculosis and it will not cure endobronchial disease. That is equally true of streptomycin in combined treatment and INH in combined treatment in a fair series of cases by now. If we are convinced—and I hope we will know in another year (we are doing a large randomized series of cases)—that isoniazid will prevent meningitis then I think we should treat primary tuberculosis regardless of the age of the child.

MR. STEENKEN: Walsh, it seems to me that everything is directed toward chemotherapy here today, and the host resistance is being neglected. If we didn't believe that host resistance has a lot to do, besides chemotherapy, why vaccinate with BCG? You might as well

wait till everybody develops tuberculosis and then treat them with chemotherapeutic agents.

DR. MCDERMOTT: Well, as a matter of fact, in all seriousness, I think that is a possible method for increasing host resistance and I think it is a method that we will hear considerably more about in the future. We have not polled the panel on this point. Ross, how do you feel about it?

DR. MCLEAN: Opinion and not knowledge. I would not treat primary tuberculosis in infants, nor would I treat even in young individuals who turned from negative to positive reactors, without some other evidence of progressive disease.

DR. MCDERMOTT: Guy, opinion?

DR. YOUMANS: I think I've already expressed myself, partially, but I'd still like to ask why you have to wait until people get sick until you treat them to keep them from being sick?

DR. MCDERMOTT: Carl?

DR. TEMPEL: We don't do it. Each year in our hospital with 1,200 patients there are always a number of nurses who convert to positive. We've never used it and we follow them along adequately and we feel that's the way to manage it.

DR. MCDERMOTT: Bill?

MR. STEENKEN: I agree with Paul Bunn.

DR. MCDERMOTT: Nick?

DR. D'ESOPO: No, I would not. I would just like to add that, once you decide to treat one of these people, I think you've got to treat for eight or twelve months and the patient won't tolerate any toxicity, dizziness, and so forth. I think that's the great objection. We don't know enough to go that far.

DR. MCDERMOTT: John?

DR. JONES: I would not treat them. Would you?

DR. MCDERMOTT: Yes, I'd treat them; that is, I think in the U. S. I would treat definitely in a situation as outlined by Dr. Lincoln, and I believe I would treat children. Moreover, I think the method may have very widespread application along the lines indicated by Bill Steenken. Bill said that, instead of giving them BCG, why don't you let them get a primary infection and then treat. And I would favor just that in areas where, unlike the U. S., the incidence of tuberculosis is very high.

DR. YOUMANS: One question on that, Walsh. To follow that through to its logical conclusion, we should not give BCG; we should just inoculate with virulent organisms and then give them chemotherapy.

DR. MCDERMOTT: For ethical reasons that's obviously not possible, but there is no reason why we shouldn't take advantage of nature and study the situation as it arises.

But it comes time to sum up, and I think the situation can be summed up about as follows:

The members of the panel are in agreement that the use of two drugs is better than one drug alone—specifically better than streptomycin alone or isoniazid alone. The consensus seems to be that streptomycin-PAS is definitely the first choice as antimicrobial therapy for long continued therapy. In so far as isoniazid is concerned, opinions were mixed. It was pointed out that meningitis was prevented in miliary tuberculosis; it can be mentioned that relapse is prevented in miliary tuberculosis; but the belief was that, as a drug alone, isoniazid was not the equivalent of streptomycin-PAS for the long pull. Finally, I think the panel did not favor the notion of using antimicrobial therapy, with the exception of Dr. Youmans and myself, for tuberculosis manifested solely by a change in hypersensitivity to tuberculin.

I see our time is up and I would like to thank the members of the panel and the audience.

NOTES

APPOINTMENT OF DR. JULIUS L. WILSON

Dr. Julius Lane Wilson, director of clinics and professor of medicine at the Henry Phipps Institute of the University of Pennsylvania, Philadelphia, since May, 1952, has been named first director of medical education for the American Trudeau Society, medical section of the National Tuberculosis Association.

Dr. Wilson took over his new duties on July 1, on a part-time basis. He will continue to have his office at the Henry Phipps Institute, where he will continue with some of his teaching and administrative responsibilities.

As director of medical education for the ATS, he is in charge of the Society's educational activities, particularly as they pertain to the teaching of pulmonary diseases to both graduate and undergraduate physicians.

A native of Pawling, New York, Dr. Wilson was educated at Princeton University and received his medical degree from the Johns Hopkins University School of Medicine in 1923, later pursuing postgraduate study in Berlin and Vienna.

In addition to teaching at Henry Phipps Institute, Dr. Wilson has also taught at the Yale and Tulane University Medical Schools. Before going to New Orleans in 1938, he was resident physician at the W. W. Winchester Memorial Hospital, West Haven, Connecticut, and at the New York State Tuberculosis Hospital at Ray Brook. In New Orleans, he was visiting physician, Charity Hospital of Louisiana, and head of the section on chest diseases at the Ochsner Clinic.

Long active in tuberculosis work, Dr. Wilson has served as president of the American Trudeau Society, the Louisiana Tuberculosis Association, and the Southern Tuberculosis Conference, and as a member of various ATS committees.

ANNUAL MEETING OF THE AMERICAN TRUDEAU SOCIETY—1954

The American Trudeau Society, medical section of the National Tuberculosis Association, invites the submission of scientific papers for presentation at its next annual meeting in Atlantic City, New Jersey, May 17 to 21, 1954.

Abstracts

Abstracts of papers to be offered for presentation should be submitted in *duplicate* not later than December 1, 1953, with an absolute deadline of January 1, 1954, to Dr. Julius L. Wilson, Chairman of the Medical Sessions Committee, Henry Phipps Institute, 7th & Lombard, Philadelphia 47, Pa.

Abstracts should be limited to a 300-word summary including important data and conclusions. Charts and tables should be attached to aid in the selection of papers.

The names, titles, and complete addresses of the senior author and co-authors should be included in each abstract. The author who is to present the paper must be the first author listed in the abstract.

All abstracts and papers will be reviewed by the Medical Sessions Committee and, when necessary, by experts in special fields in order to select those containing the most interesting material. Final selection will be on a competitive basis.

Subjects for presentation may include all scientific aspects of tuberculosis and nontuberculous respiratory and cardiopulmonary disease as well as the results of investigative work bearing on these subjects.

Those wishing to present subjects of a confidential nature from the armed forces or other sources must clear the material through official channels *before* submitting the abstracts to the Chairman of the Medical Sessions Committee.

Papers

Subsequent to review of the abstracts by the Medical Sessions Committee, papers will be chosen on a competitive basis from among the abstracts for presentation at the annual meeting. Authors will be notified by February 1, 1954, if their papers are to be read.

A double-spaced typewritten manuscript must be prepared in *duplicate* to be presented to the moderator of the session at the time the speaker presents his paper at the annual meeting.

Papers presented at the annual meeting must be original contributions which have not previously been presented or published. All such papers should be considered as belonging exclusively to the National Tuberculosis Association and should not be submitted for publication elsewhere without the advance permission of the National Tuberculosis Association.

Abstracts of all papers given at the annual meeting will be published in the annual *Transactions* of the National Tuberculosis Association. All papers will be submitted to THE AMERICAN REVIEW OF TUBERCULOSIS, but publication in the REVIEW will be subject to the decision of the Editor.

The time allotted for presentation of papers at the annual meeting will be strictly limited by the committee in order to permit adequate discussion.

Participants in the program are reminded of the fact that travel expenses to the annual meeting are not paid by the National Tuberculosis Association.

SYMPOSIUM IN SYSTEMIC MYCOSES PLANNED

The Southwestern Medical School of the University of Texas in association with the Dallas Southern Clinical Society and under the auspices of the Postgraduate School of Medicine of the University of Texas, the Texas State Medical Association, and the Texas Chapter of the American Academy of General Practice announce a postgraduate course in systemic mycoses to be presented at Dallas, Texas, on January 18–20, 1954. Guest speakers include Dr. C. E. Smith, Dr. Norman Conant, Dr. M. L. Furcolow, and Dr. Libero Ajello. For further information on this course write to Dr. John S. Chapman, Assistant Dean, Graduate and Postgraduate Education, Southwestern Medical School of the University of Texas, 2211 Oak Lawn Avenue, Dallas, Texas.

NEWS ITEM

The Trudean Sanatorium, which celebrates its 70th anniversary next year, has just prepared a brief pamphlet entitled "Answers to *Questions* from Physicians about Trudeau Sanatorium." The leaflet is based on questions most frequently asked by physicians about the sanatorium and should be useful to any physician who sees tuberculosis patients. Copies may be obtained by writing to Dr. Roger S. Mitchell, Clinical Director, Trudeau Sanatorium, Trudeau, New York.

THE AMERICAN REVIEW OF TUBERCULOSIS

ABSTRACTS

Edited by LAWRENCE B. HOBSON

VOLUME 68 NOVEMBER 1953 ABST. No. 5

CLINICAL STUDIES, TUBERCULOSIS

Miliary Tuberculosis Following Corticotropin.—Experimental work in animals has demonstrated that corticotropin (ACTH) and/or cortisone enhances the evolution and development of tuberculous lesions. A case of miliary tuberculosis, proved by postmortem examination, developed during extensive corticotropin and cortisone therapy for acute disseminated erythematosus. Before treatment this patient had a thorough but negative examination for tuberculosis; within four months after starting hormone therapy, widespread, fulminating, widely disseminated tuberculosis involved the lungs, liver, lymph nodes, and bone marrow. In the lungs, necrosis and caseation were marked in the tubercles and there was no fibroblastic inflammatory reaction around the lesion. This supports the thesis that the impaired granulation and fibrotic tissue formation in patients receiving corticotropin or cortisone may be responsible for their harmful effects.—*Appearance of miliary tuberculosis following therapy with ACTH and cortisone in a case of acute disseminated lupus erythematosus, A. G. Davidson, L. Fox, & J. J. Gold, Ann. Int. Med., April, 1953, 38: 852.*—(*T. H. Noehren*)

Acute Miliary Tuberculosis During Cortisone Therapy.—A 53-year-old man was admitted to the hospital in severe heart failure and with evidence of recurrent rheumatic carditis. Conservative measures produced improvement but fever persisted and he developed a lymphocytic polyserositis. No tubercle bacilli could be demonstrated in the exudate and no infection with any organism could be found. He was given 2.0 gm. of cortisone over an eighteen-day period, during which he improved. Immediately after the hormone was discontinued, the patient grew worse with somnolence, recurrent fever, and finally coma. He died eight days after treatment was stopped. At autopsy, there was miliary tuberculosis with tuberculous ulceration in the intestines; the heart showed hypertrophy and carditis, probably rheumatic, but no endocarditis. This case afforded another example of the grave risk in using cortisone even for patients with inapparent tuberculosis.—*Granulie developpée chez un patient atteint de polysérosite rhumatismale traite à la cortisone, J. Pirart, Acta clin. belg., 1953, 8: 63.*—(*L. B. Hobson*)

Treatment and Progression in Minimal Tuberculosis.—A total of 389 ambulatory cases of minimal pulmonary tuberculosis in patients fifteen to seventy-one years old was observed for one to six years. There were 214 patients with exudative lesions and 48 with productive lesions, neither of which had received any special treatment. Infiltrative-exudative processes had an unfavorable prognosis as compared with fibrous lesions. Among the former, 54 per cent progressed, 16 per cent remained unchanged, and 30 per cent regressed; among the latter, the figures were 18.7, 73.0, and 8.3 per cent, respectively. Tomography permitted more accurate anatomic diagnosis of the minimal lesions. Roentgenographically, 28 of 49 cases were considered to be exudative. Tomography revealed that this was correct in only 16 cases. A search for tubercle bacilli in gastric and pulmonary contents in 612 cases yielded only 8 per cent positive results in minimal lesions. The figure rose to 37 per cent in infiltrative-exudative lesions. The prognosis of minimal lesions was less favorable in younger patients. Progression rates rose from zero in the more than 50-year

age group to 39.5 per cent in the 41- to 50-year group, and 73 per cent in the 15- to 20-year group. In the 15- to 25-year age group, the prognosis was less favorable among women. Both streptomycin and pneumothorax reversed the process. Regressions reached 71.3 per cent among 87 patients treated with pneumothorax and 65 per cent among 40 patients treated with streptomycin as compared with 23 per cent among 262 patients who did not receive any special treatment. Almost one-fourth of the patients treated by collapse got worse with bilateral extension of the disease. Approximately one-third of the streptomycin cases relapsed, usually after discontinuance of the drug. In 5 cases, streptomycin resistance developed.—*Tratamento e prognóstico das lesões minimas da tuberculose pulmonar, J. Rosemberg, J. Aun, & J. Cerqueira do Amaral, Rev. brasil. tuberc., January–February, 1953, 21: 51.*—(*A. A. Moll*)

Pathogenesis of Pulmonary Tuberculosis.—Animal experiments and pathologic-anatomic observations on humans with tuberculosis showed that in the third week after the infection with tubercle bacilli the disease lymph nodes start to penetrate into the bronchial wall, erode the mucous membrane, and thence spread bacilli bronchogenically. Massive aspirations occur four to eight weeks after the beginning of the disease, when large caseous hilar and paratracheal lymph nodes empty their necrotic content into the bronchial lumen. This lymphadeno-bronchogenic aspiration is frequently followed by extensive pulmonary infiltrations, which usually take a benign course. Such a necrotic lymph node may perforate simultaneously into a bronchus and into the pleural cavity, into the pleural cavity only, into the pericardium, or into the esophagus. Many lymphadeno-bronchogenic infiltrations located in the subapical field are described as Assmann infiltrates and Simon foci. Also, the reactivation of chronic pulmonary tuberculosis starts usually in intrathoracic lymph nodes.—*Pathogenese der Lungenphthise, Ph. Schwartz, Wien. klin. Wchnschr., February 20, 1953, 65: 157.*—(*G. C. Leiner*)

Pulmonary Tuberculoma.—The roentgenographic features of tuberculoma, based on a study of 19 cases of proved lesions, may be summarized as follows: (*1*) the presence in the lung of a round, ovoid, or lobulated area of increased density, which may be single or multiple; (*2*) evidence on serial roentgenograms that the lesion is enlarging over a period of time; (*3*) a tendency toward central cavitation; (*4*) in some instances the presence of "fleeky" calcification within the tumor; and (*5*) the location of the lesion beneath and close to the pleural surface of the lung, most commonly in the apical segment of an upper lobe or superior segment of a lower lobe. In the presence of single or multiple tuberculomas, the remaining lung fields may show evidence of a minimal degree of tuberculous infection, old or recent, without enlarged intrathoracic lymph nodes or significantly collapsed lobes or segments of the lung. The general trend in treatment of tuberculoma is toward surgical intervention in order to remove the potential source of tuberculous spread and to establish the exact nature of the pulmonary lesion.—*Roentgen features of pulmonary tuberculoma, C. C. Wang, Radiology, April, 1953, 60: 536.*—(*W. J. Steininger*)

Primary Cutaneous Tuberculosis.—In a period of five years, 28 cases of primary tuberculosis of the skin, mouth, or eye have been observed. With one exception, the patients were all children less than twelve years old. The infection was situated on the skin in 20 cases, on the conjunctiva in 5, and in the mouth in 3. In 22 cases, direct histologic or bacteriologic proof and, in 6 cases, strong circumstantial evidence of a tuberculous etiology was obtained. In 11 of the 20 cases with skin lesions, there was a history of contact with an infective adult and a history of trauma in 10 cases. Only one case presented with a systemic illness. In the other 19, a local lesion was detected in an otherwise well child. In 6, the conspicuous lesion was on the skin, while in 13, there was a swelling of a lymph node. In the 10 cases with a history of injury, the usual story was that of a skin cut or abra-

sion which failed to heal; this was followed by a painless swelling of the regional lymph nodes. In the nontraumatic cases, most of the lesions were on exposed surfaces of the skin. Most were 0.5 to 1.0 inch in diameter, roughly ovoid, with a depressed center and a raised edge. In several cases, there were scattered nodules within a zone surrounding the main lesion. Of the 5 patients with conjunctival lesions, 3 first complained of irritation of the eyes; 3 had enlargement of the preauricular glands. The lesion was either a fungating mass of granulations or a shallow ulcer with a yellow base and much surrounding edema. There were 3 lesions in the mouth, all conspicuous. In all 28 cases in this series, the regional nodes eventually softened to form abscesses.—*Recognition of primary tuberculous infection of skin and mucosae, F. J. W. Miller, Lancet, January 3, 1953, 1: 5.—(A. G. Cohen)*

Tuberculous Salpingitis.—Of 41 cases diagnosed histologically as tuberculous salpingitis, 12 had concentrically laminated iron-reacting Schaumann bodies in the tubal lesions and 11 of these also had acid-soluble birefringent crystalline bodies. In 100 control cases of nontuberculous salpingitis, only one laminated body was found. In 4 of the 12 cases the diagnosis was confirmed by finding tubercle bacilli in the affected fallopian tube. The presence of Schaumann bodies in the fallopian tube, even in the absence of histologic proof of tuberculosis, suggests that there has been an antecedent tuberculous salpingitis (Author's summary).—*Schaumann bodies in tuberculous salpingitis, J. C. Burne, J. Path. & Bact., January, 1953, 65: 101.—(H. J. Henderson)*

Diagnostic Bronchial Lavage.—No case should be diagnosed as tuberculous unless the presence of tubercle bacilli is demonstrated. Bronchial lavage is valuable for this purpose in patients with little or no sputum. A negative bacteriologic report should carry the same weight as a positive one. Cases of doubtful activity do not quite fit the clinical conception of "minimal lesions"; perhaps a group of "only residual shadows" should be added to the present classification. A tuberculin test (1:10,000) might distinguish between patients with only residual shadows and those with potentially progressive lesions. Among 16,351 patients from whom bronchial washings were obtained, 4,758 (29 per cent) were considered to have only residual shadows and all were bacteriologically negative. Among 3,971 considered to have minimal lesions, 12.2 per cent were bacteriologically positive, as compared with 43.2 per cent among 1,764 cases with moderately advanced lesions and 68.2 per cent among 181 cases with advanced lesions. There were few moderately advanced cases in the series because in such cases sputum is usually plentiful and no bronchial lavage is needed. In Brazilian tuberculosis hospitals, approximately 70 per cent of the cases are advanced, perhaps 25 per cent moderately advanced, and only 5 per cent are minimal cases. This distribution is a warning about the effectiveness of the tuberculosis campaign as carried out so far.—*Diagnóstico de tuberculose e lavado brônquico, M. Fontes Magarão, Rev. brasil. tuberc., January-February, 1953, 21: 67.—(A. A. Moll)*

Bronchospirometry.—To define the general effects of pulmonary disease on function, the specific effects of pleural, parenchymal, bronchial, and pulmonary vascular disease were examined separately. The highly variable results in pulmonary conditions, which usually involve several of these factors, were interpreted on the basis of the findings. The changes resulting from medical treatment, pulmonary collapse, or resection, and surgical procedures designed to restore function were also analyzed to determine the effect of treatment. In the series of 1,089 individual bronchospirometric studies, most of the patients (81.5 per cent) had pulmonary tuberculosis and its complications. In bronchial asthma, split function studies were carried out before operation and after unilateral or bilateral denervation. Patients with pulmonary emphysema had bronchospirometry only when they had large bullae and greater impairment of one lung was suspected. Some patients with bronchi-

ectasis were examined only after pulmonary resection had been performed on one side. In evaluating the effect of unilateral pulmonary disease, attention was focused on oxygen uptake, which finally determines the productivity of the respiratory effort. Carbon dioxide elimination was of less interest because it is rarely a problem in unilateral disease. The relationship of oxygen uptake to ventilation and vital capacity was also examined. The degree of functional impairment determined by bronchospirometry was compared with the extent of involvement estimated by clinical and other laboratory methods. The results of split function studies in 170 cases of unilateral parenchymal disease showed slightly reduced respiratory participation by the involved lung; oxygen uptake, resting ventilation, and vital capacity were almost equally affected. The degree of impairment was less severe than anticipated from the appearance of the chest roentgenogram. A group of 127 patients with unilateral pleural complications showed a striking diminution of function on the involved side. Oxygen uptake was most defective, vital capacity was less affected, and ventilation was least impaired. In some patients minute ventilation was normal or even increased in spite of severely impaired oxygen uptake. The degree of impairment was more severe than anticipated from the appearance of the chest roentgenogram. Bronchial disease caused abnormal function only when a major bronchus was completely or almost completely occluded. Obstruction of one branch of the pulmonary artery had little effect on ventilation or vital capacity but oxygen uptake was severely impaired on the affected side. The loss of function after subtotal pulmonary resection was, on the average, equal to that after thoracoplasty of similar extent. The occurrence of pleural complications following resection made the outcome more variable and hence less predictable than the results after collapse. Among the operations designed to improve pulmonary function, decortication caused marked increase in function if the collapsed lung was not involved by pre-existing parenchymal disease. Some recovery was found following resection of pulmonary cysts. The functional improvement after bronchial reconstruction was encouraging. The results of autonomic nerve resection for the treatment of bronchial asthma or pulmonary emphysema were not good.—*Bronchospirometry: VI. Results of 1,089 examinations, E. A. Gaensler, I. R. Watson, Jr., & W. E. Patton, J. Lab. & Clin. Med., March, 1953, 41: 436.*—(*F. G. Petrik*)

Copies of Roentgenograms.—One of the most difficult problems of large roentgenological departments is finding space to file their roentgenograms. Small negative copies of roentgenograms greatly reduce the space required but facsimiles produced from copy negatives usually do not closely resemble the original. Detail is lost in the area where detail is most needed for diagnosis. An adequate setup for making good copy negatives is not complicated. The standard roentgenogram viewer serves as the copy board and any good 35-mm. or roll film camera is used for the photography. Test exposures are made using a variety of roentgenograms similar to those to be later copied. These tests determine the final adjustments in the camera distance, focus, and the standard exposure. The ideal combination of photographic films is a fast, fine-grain, low-contrast film with great exposure latitude for the intermediate copy, and a high-contrast film with as nearly a straight-line response as possible for the final facsimile. Inasmuch as facsimiles are made from only a few of the roentgenograms copied for filing, it would be highly desirable to use a type of film avilable in the laboratory rather than to resort to special material. A satisfactory copying film for the intermediate negatives would be a medium- to low-contrast protrait film. Ordinary medical roentgen film could be used for the final facsimiles. Fluorographic-type film, while usable, is not completely satisfactory for the intermediate negative because of its inherently high contrast.—*Satisfactory copies from original roentgenograms on a production basis, H. G. Morse, Am. J.*

Roentgenol., April, 1953, 69: 647.—(T. H. Noehren)

CLINICAL STUDIES, NONTUBERCULOUS DISEASES

Pulmonary Migration in Creeping Eruption.—Creeping eruption is characterized by a linear serpiginous eruption produced by animal parasites migrating in the skin. The classic lesion is a narrow, raised, erythematous lesion along the course traversed by this parasite. Once the parasite pentrates the skin, it advances in random fashion, producing a well-defined track. *Ancylostoma brazilienza*, the common dog and cat hookworm, causes most of the cases of creeping eruption in the southeastern and southern sections of this country. A patient with creeping eruption developed asthma one week after the onset of the skin lesions. Examination of the sputum revealed filariform hookworm larvae which looked like *Ancylostoma brazilienza*. It was thought that the patient's attack of asthma was caused by the pulmonary migration of the hookworm larvae. The larvae are said not to migrate beyond the site of skin penetration; the finding of larvae in the sputum of this patient for a period of twenty-four days indicates that they are not always confined to the skin. The multiplicity of respiratory symptoms and the absence of pulmonary infiltration differentiated this case from one of Löffler's syndrome. The patient approved withholding vigorous treatment of the lesions so that the disease process could be followed. The patient did not develop intestinal hookworm infection and was discharged as asymptomatic. More sputum studies should be done in patients with creeping eruption, particularly in those having respiratory symptoms associated with Löffler's syndrome.—*Demonstration of pulmonary migration of the causative organism of creeping eruption, J. P. Muhleisen, Ann. Int. Med., March, 1953, 38: 595.—(T. H. Noehren)*

Acute Plasma Cell Pneumonia.—A nine-week-old male child died from acute interstitial plasma cell pneumonia. On histologic examination of the lungs, intracellular formations were found; these were believed to be *Pneumocystis carinii*. These protozoa, previously found in this disease, occur spontaneously in rats.—*Ein Beitrag zur Aufklärung der Aetiologie der akuten interstitiellen plasmazellulären Pneumonie, H. Moritsch, Wien. klin. Wchnschr., April 10, 1953, 65: 280.—(G. C. Leiner)*

Pleuropulmonary Tularemia.—A 42-year-old Negro with bronchopneumonia and pleural effusion was seen. The serum agglutinin titer for *Pasteurella tularensis* rose to 1:5,120 by the nineteenth day of the disease. The patient developed peripheral polyneuritis, probably secondary to absorption of bacterial toxins. The pleuropulmonary infection was treated successfully with aureomycin.—*Pleuropulmonary tularemia complicated by peripheral neuritis, M. Raphael & A. E. Anderson, A. M. A. Arch. Int. Med., February, 1953, 91: 278.—(G. C. Leiner)*

Varicella Pneumonia.—Clinically, varicella pneumonia has an alarmingly rapid onset of dyspnea, tachypnea, fever, and cough within two to six days of the first appearance of the chickenpox rash. Gross hemoptysis, usually of several ounces of blood, may occur. The patients are cyanotic with marked tachycardia. Vasomotor collapse occurs in some cases and is occasionally fatal. Moist rales are scattered throughout the lungs with transient areas of bronchovesicular and bronchial breathing. In some cases the symptoms of the pulmonary complication precede the physical signs by several hours. Pleurisy may occur. Leukocyte counts range from 4,000 to 14,000, with a slight shift to the left in the Shilling-Arneth count. Blood cultures are sterile. Roentgenograms of the chest uniformly show a diffuse nodular pneumonic infiltration. The findings slowly resolve during a period of several weeks. Detailed postmortem observations, available in 4 cases, show pulmonary changes similar to those in other types of viral pneumonia. Consistently, there are swelling, proliferation, and desquamation

of the septal cells to form large mononuclear phagocytes; these form the usual cellular exudate. Alveoli are lined with hyaline membranes, and foci of necrosis, hemorrhage, fibrinous exudation, and arteriolitis are common. Bacteria and polymorphonuclear leukocytes are rare. In 2 cases, characteristic type A intranuclear inclusion bodies of varicella have been found in the alveolar septal cells and macrophages, and in bronchiolar epithelial cells. These inclusion bodies have also been observed in the spleen, liver, adrenals, tracheobronchial lymph nodes, the epidermis, and in fibroblasts and endothelial cells of the dermis and subcutaneous tissues in one case. Chickenpox has been noted on the surfaces of the pleura, liver, and spleen. A 36-year-old man with severe chickenpox recently had extensive pneumonia and complicating shock, heart failure, homonymous hemianopsia, and pulmonary suppuration. The clinical features of the pneumonia, presumably due to varicella virus, were consistent with those described in previous cases.—*Varicella pneumonia with shock and heart failure, M. Rosecan, W. Baumgarten, Jr., & B. H. Charles, Ann. Int. Med., April, 1953, 38: 830.*—(*T. H. Noehren*)

Varicella Pneumonia.—In only a few reported cases of varicella pneumonia has the varicella virus appeared to cause the pulmonary complication. Three adults developed extensive nodular pulmonary infiltrations while having chickenpox. The lung lesions disappeared at the same time as the skin lesions.—*Varicella pneumonia, S. Saslaw, J. A. Prior, & B. K. Wiseman, A. M. A. Arch. Int. Med., January, 1953, 91: 35.*—(*G. C. Leiner*)

Histoplasmosis Simulating Tuberculosis.—Chronic bilateral upper lobe pulmonary histoplasmosis of mixed bronchopneumonic and cavitary types was diagnosed in a 56-year-old white man from whose sputum *Histoplasma capsulatum* was repeatedly cultured. Interstitial pneumonitis, discrete or confluent areas of lobular pneumonia, miliary and larger nodules, granulomata, caseation necrosis, abscesses or cavities, fibrosis, and calcification have been described in patients with histoplasmosis. There is no characteristic abnormality in the chest roentgenograms. Lesions resembling apical reinfection tuberculosis, like those in the present case, were demonstrated in only 4 of 65 patients with proved pulmonary histoplasmosis. In only 3 cases was pulmonary cavitation present and in these the cavities may not have been due to histoplasmosis. Proved cavitation has been demonstrated in the surgical specimens in each of 3 reported cases of patients treated by pulmonary resection. Pulmonary symptoms depend upon the location and nature of the lesions. Histoplasmosis has been described as a chronic febrile illness in an emaciated patient having anemia, leukopenia, generalized lymph node enlargement, splenomegaly, hepatomegaly, and ulcerative or granulomatous lesions of the nose, mouth, pharynx, or larynx. The present patient had a chronic illness and occasional short periods of fever but none of the other classic findings. This suggested that the disease was limited to the lungs. Since patients with histoplasmosis not infrequently have another disease also, a careful search was made but none was found. This is the first case of proved histoplasmosis reported in a life-long resident of New York State who had never traveled outside of the state.—*Histoplasmosis, with review of the literature and report of a case proved by culture, with involvements of the upper lobe of each lung simulating active bilateral apical pulmonary tuberculosis, J. Monroe & J. M. Kurung, Ann. Int. Med., February, 1953, 38: 206.*—(*T. H. Noehren*)

Baritosis.—Baritosis, a "benign" or "nonspecific" form of pneumoconiosis, occurs chiefly among the baryta miners of Italy, who inhale finely ground particles of barium sulfate. In baritosis there is no respiratory incapacity, the only evidence of the condition being the roentgenographic demonstration of small, sharply circumscribed nodules evenly distributed throughout the lung fields. Bari-

tosis has not been reported often in the United States in spite of the large number of workers exposed to barium dust. The distribution of the nodules in baritosis is similar to that seen in silicosis, which should be considered in the differential diagnosis. A case of baritosis and anthracosilicosis studied post mortem occurred in a patient who had worked in a hard coal mine in Pennsylvania and in a small lithopone plant where he was exposed to finely divided particles of barium sulfate.—*Baritosis: Report of a case, E. P. Pendergrass & R. R. Greening, A.M.A. Arch. Indust. Hyg. & Occup. Med., January, 1953, 7: 44.*—(*T. H. Noehren*)

Pulmonary Granulomatosis.—A 53-year-old white woman complained of cough and progressive dyspnea of three years' duration. A chest roentgenogram revealed diffuse ground-glass haziness throughout both lung fields and a shadow in the right upper mediastinum. Two years later a chest roentgenogram showed slight increase in the diffuse haziness of both lung fields. A biopsy from the lingula disclosed platelike crystals, often surrounded by granular blue-staining material, which probably represented calcium. Around these masses, fibrous tissue proliferation and foreign-body giant cells were seen, some of the giant cells containing similar crystals within their cytoplasm. The crystals were similar to those of paradichlorobenzene, an insecticide, which the patient had used repeatedly for twelve to fifteen years in large amounts as a moth eradicator. A rabbit which died after one week of exposure to paradichlorobenzene vapors was found to have acute pneumonia of both lungs; crystals were present in the exudate similar to those in the patient's lungs.—*Pulmonary granulomatosis following extensive use of paradichlorobenzene, R. W. Weller & A. J. Crellen, A. M. A. Arch. Int. Med., March, 1953, 91: 408.*—(*G. C. Leiner*)

Kerosene Pneumonitis.—Four infants were poisoned by ingesting kerosene. The roentgenologic changes produced in the lungs by kerosene generally comprise a bilateral uniformly disseminated bronchopneumonitis which clears in one to three weeks, usually a week or two after the clinical cure. The amount of kerosene ingested determines the degree of injury produced in the lungs. Since kerosene can be detected in the lungs as early as thirty minutes after ingestion, roentgenograms should be taken early to determine the extent of the damage. Pneumonitis is the most frequent finding, but emphysema, pneumothorax, pleurisy, pneumonia, and fluid may appear. Roentgenologic changes precede clinical manifestations and often marked changes are seen in films in the absence of physical findings. The same changes are produced by kerosene, furniture polish, turpentine, and cleaning fluid. In mild cases, patchy consolidation is observed in the cardiophrenic angles. In more severe cases, diffuse, opaque consolidation extends from both hilar areas to the periphery of both lung fields; this consolidation later resolves in the form of fine mottled densities. The number of fatal cases is small and is variously estimated from 2 to 10 per cent.—*Roentgenography of kerosene poisoning (chemical pneumonitis), J. Gershon-Cohen, L. S. Bringhurst, & R. N. Byrne, Am. J. Roentgenol., April, 1953, 69: 557.*—(*T. H. Noehren*)

Systemic Lupus Erythematosus.—Systemic lupus erythematosus is an important "collagen disease," the pathology and pathogenesis of which are poorly understood; its etiology is unknown. Lesions of the respiratory system are common in systemic lupus erythematosus and often dominate the clinical picture. The upper respiratory tract is seldom involved. Pleuritis with effusion is probably the most frequent manifestation of respiratory involvement, although interstitial or bronchopneumonic pneumonitis is common. Abnormal urinary findings are so universal that their absence casts doubt on the diagnosis of lupus erythematosus. Proteinuria occurs in practically all cases, cylindruria and microscopic hematuria in approximately 70 to 80 per cent. The simultaneous occurrence in the urine of protein, erythrocytes, and red-cell casts, oval fat bodies, broad fatty and waxy casts may

prove to be peculiar to this disease. The amount of renal disability oddly is far less than might be expected from the urinary and histopathologic findings, and renal failure is not an important cause of death. Leukopenia and, more commonly, anemia are frequent and a reversal of the albumin-globulin ratio occurs often. A peculiar type of cell, termed the "L.E. cell," occurs in the buffy layer of bone marrow taken from patients with acute and subacute disseminated lupus erythematosis. This cell, described as a mature polymorphonuclear leukocyte, contains a mass of homogeneous, purple-staining material, presumably of nuclear origin. A specific plasma factor seems to be responsible for "L.E. cell" formation, and the activity of the plasma factor appears to be related to the severity of the disease. "L.E. cell" formation can be induced by incubating the plasma of lupus patients with cells from the marrow of normal persons. The specificity of this "L.E. cell" phenomenon is well documented. Laboratory findings are all important in the diagnosis of this disease.—*Systemic lupus erythematosus: A review of the literature, S. W. Ross & B. B. Wells, Am. J. Clin. Path., February, 1953, 23: 139.*—(*J. S. Woolley*)

Pulmonary Hemosiderosis.—Idiopathic pulmonary hemosiderosis is a rare disease affecting children between the ages of a few months and sixteen years; only one case has been reported in an adult. The patients have recurrent attacks of fatigue, cyanosis, fever, pallor, and increasing dyspnea which usually occur suddenly and are associated with a marked iron-deficiency anemia suggesting hemolysis. Coughing and vomiting are often prominent in the acute attacks; hemoptysis and hematemesis have been reported in many cases. The attacks last for a few days but may pass into a subacute stage which persists for longer periods. In long-standing cases, evidence of right ventricular hypertrophy is usually present and clubbing of the fingers may occur. The pulmonary changes in roentgenograms may be characteristic, the commonest feature being mottled shadows in the hilar regions and diffuse speckling throughout the peripheral lung fields. Post-mortem examination of the lungs reveals extensive diffuse hemorrhages with generalized invasion of the alveoli by macrophages containing hemosiderin; there is no evidence of hemosiderosis elsewhere in the body. Other notable features are diffuse pulmonary fibrosis and degeneration of the elastic tissue in the alveolar walls and in the blood vessels of the lung. These changes in the elastic tissue of the lung have been suggested as the primary causes of the disease. The clinical diagnosis was confirmed in a two-year-old child by aspiration lung puncture which yielded macrophages loaded with hemosiderin granules. The sputum or gastric washings should be performed for macrophages containing hemoseridin in patients with obscure iron-deficiency anemias associated with pulmonary findings. If such examinations are negative, an aspiration lung puncture should be considered.—*Use of aspiration lung puncture in diagnosis of idiopathic pulmonary hemosiderosis, S. S. Gellis, J. L. D. Reinhold, & S. Green, A. M. A. Am. J. Dis. Child., March, 1953, 85: 303.*—(*M. J. Small*)

Periarteritis Nodosa and Sarcoidosis.—Five proved cases of periarteritis nodosa and one of sarcoidosis illustrate the similarities of the etiologic, clinical, biochemical, histologic, and therapeutic aspects of these entities. Periarteritis nodosa and sarcoidosis probably are not two distinct and separate entities but constitute different stages of the same disease. This disease should be called "hypersensitivity granuloma," acute or chronic, perivascular or extravascular. The so-called collagen diseases are a heterogeneous group requiring a more concise classification (Author's summary).—*The relationship between periarteritis nodosa and sarcoidosis, A. Jackson & I. Kass, Ann. Int. Med., February, 1953, 38: 288.*—(*T. H. Noehren*)

Bronchiectasis.—Early bronchographic studies were performed on 60 consecutive pneumonia patients who had no history of previous pulmonary disease. Bronchial ab-

normalities were observed in 25 of the 60 patients. The etiologic agents of the pneumonias were studied and related to the occurrence of atelectasis and bronchial disease. Streptococcal pneumonias were accompanied by significant bronchopathy in a large percentage of cases. The incidence of demonstrable bronchial abnormalities in primary atypical pneumonia was lower but still of considerable magnitude. Analysis of the material appeared to indicate that atelectasis does not cause bronchiectasis. Rather, both the atelectasis and the bronchiectasis resulted from a common factor, i.e., injury to the bronchus. Patients showing initial bronchial abnormalities had serial bronchograms which demonstrated a great tendency for the abnormal bronchi to revert to normal. In practically all of the patients with bronchiectasis, the status reversed completely or improved considerably. The safety of instilling comparatively large amounts of iodized oil (Lipiodol) early in the course of pneumonia for any such study was demonstrated (Authors' summary). —*Bronchiectasis: A bronchographic study of sixty cases of pneumonia, A. L. Bachman, W. R. Hewitt, & H. C. Beekley, A. M. A. Arch. Int. Med., January, 1953, 91: 78.*—(*G. C. Leiner*)

Respiratory Exercises for Emphysema.—The clinical results following the use of asthma exercises for patients with all types of chronic obstructive but nontuberculous chest diseases suggested that such treatment was only slightly beneficial to patients with emphysema. Special exercises were then developed for the treatment of emphysema. Since there is little inspiratory obstruction, the breathing pattern was altered; the strength and control of the abdominal musculature was developed and the patient was trained to use these muscles to produce an active forceful expiratory phase. The amount of air inhaled during the succeeding passive inspiratory cycle depended upon the elastic recoil of the entire chest and abdomen. Reversing the active phase interrupted hyperinflation of the lungs and allowed more complete air exchange. This altered respiratory pattern became automatic and habitual with practice and could combat exertional dyspnea. Because of the progressive irreversible loss of lung elasticity in emphysema, some disability often remained after the patient had achieved maximal benefit from the exercise. This treatment of emphysema was shown to have advantages over asthma exercises and potentially has permanent value when the altered breathing habits persist. The mobility of the chest and diaphragm are restored to a variable degree through emphasis on expiration. The breathing pattern is initially less vigorous and is more practical for constant use; it can be used voluntarily as an immediate therapeutic procedure for dyspnea or undue exertion. The method employs no external agents. It is particularly applicable to patients with severe cor pulmonale because it can be graded within their limitations and still be of value.—*Respiratory exercises for chronic pulmonary emphysema, M. E. Miller, Bull. Johns Hopkins Hosp., March, 1953, 92: 185.*—(*J. S. Woolley*)

Dust Clearance from Lung.—Most of the dust particles which lodge in an alveolus are removed by the ciliated epithelium of the bronchial passages. Alveolar macrophages ("dust cells") are believed to aid in carrying particulate matter from the respiratory membrane to the bronchiolar epithelium. These cells, varying in number, distribution, and amount of pigment, are frequent in lung sections which show little active inflammation. To determine the relationship between this pattern and the excursions of alveolar tissue, lung sections from 87 adult persons were consecutively autopsied. Special attention was given to the presence or absence of alveolar macrophages, their numbers, and their relationship to bronchi, vessels, scars, atelectasis, and edema fluid. Cases were excluded if the macrophages were associated with polymorphonuclear leukocytes, leaving 43 cases (50 per cent) with alveolar macrophages which were unrelated to active inflammation. In most instances atelectasis was the underlying cause for the accumulation of macrophages. Other demonstrable causes were alveolar

edema, thickened alveolar walls, proximity to bronchi, vessels, or scars. Reduced excursion of the alveolar walls was the common factor in all instances in which causes were recognized. A thin, uninterrupted film of protein-containing fluid may cover the respiratory membrane from the alveolus to the alveolar duct and the ciliated epithelium of the bronchiole; with each respiration the "dust" cells may move toward the bronchiole, floating on this film. Any appreciable reduction in the excursions of alveolar tissue should, by this hypothesis, lead to alveolar stasis and adversely affect the dust-removal mechanism.—*The mechanism of dust clearance from the lung: A theory, P. Gross, Am. J. Clin. Path., February, 1953, 23: 116.—(J. S. Woolley)*

Bone Marrow in Pulmonary Disease.—Histologic examination of the sternal marrow was done in 24 patients with diffuse pulmonary lesions. Nine showed a pathologic lesion in the marrow; of these, 3 had miliary tuberculosis, 2 had sarcoidosis, 2 had histoplasmosis, one had amyloidosis, and in one the disease remained undiagnosed. In 15 of the 24 patients the marrow was normal histologically; several of these had diseases limited to the lung, such as pulmonary fibrosis. Bone marrow studies in 25 patients with far advanced pulmonary tuberculosis did not reveal any lesions. Histologic examination of the bone marrow is indicated whenever a disseminated granulomatous disease is suspected or when a diagnosis of diffusely distributed pulmonary lesions cannot be made.—*Involvement of bone marrow in diffuse pulmonary disease, A. S. Weissberger & R. M. Dumme, A. M. A. Arch. Int. Med., February, 1953, 91: 212.—(G. C. Leiner)*

Osteoarthropathy in Lung Malignancies.—Chronic pulmonary disease has most frequently caused osteoarthropathy, but these bone changes have been noted often in cases of congenital heart disease, arteriovenous fistula, and subacute bacterial endocarditis. They have been less frequently described in cases of chronic liver disease, chronic intestinal infections, myxedema, polyposis, aortic aneurysms, nasopharyngeal carcinoma, thymic carcinoma, leukemia, and pulmonary blastomycosis. Grossly, osteoarthropathy is essentially proliferative subperiosteal osteitis surrounding the shaft of the bones, primarily the long bones. In advanced cases, the clavicle, rib, scapula, and veterbrae may become involved. Both the soft tissues and the bone proliferate. Although symptomatic regression of the osteoarthropathy frequently occurs, only a few cases show roentgenographic evidence that the newly formed bone is resorbed; the soft tissue swelling around the joints often decreases. Clubbing of the fingers is present in practically all cases of pulmonary osteoarthropathy. The exact relationship of these two processes is not clear but their frequent association indicates a parallel pathogenesis. Many believe hypertrophic osteoarthropathy is an advanced stage of clubbed fingers. In the latter, the change is connective tissue thickening with no change in the terminal phalanges until late, when the bone is absorbed. In advanced cases, only the base of the terminal phalanx remains. Hypertrophic osteoarthropathy and clubbing of the fingers are asymptomatic in patients with chronic pulmonary suppuration or congenital heart disease. In contrast, they are usually quite painful in patients with carcinoma of the lung. With this latter process the periosteal changes are more acute and the proliferation is more rapid; *acute* pulmonary osteoarthropathy seems an appropriate descriptive term. None of the many etiologic theories of pulmonary osteoarthropathy is satisfactory. Attempts to reproduce these bone changes experimentally have been unsuccessful. The purpose of this study has been to determine whether there was any relationship between osteoarthropathy and the type and location of the pulmonary malignant lesion. Among 139 cases of carcinoma of the lung, there were 14 cases of acute pulmonary osteoarthropathy. In all 14 cases the initial complaint was referable to the painful joints. In 13 cases the tumor was in the periphery of the lung. The size of the tumor and the type of the malignant cells apparently played no role in the development

of osteoarthropathy. It was also apparent that pulmonary infection had no part in the pathogenesis of osteoarthropathy associated with pulmonary malignant disease.—*Hypertrophic osteoarthropathy in pulmonary malignancies, E. S. Ray & H. P. Fisher, Jr., Ann. Int. Med., February, 1953, 38: 239.*—(*T. H. Noehren*)

Pulmonary Embolism Without Infarction.—Clinical and experimental studies show that simple pulmonary embolism may occur without pulmonary infarction. Anatomically, the lungs possess a dual blood supply, the pulmonary and the bronchial arteries, the latter increasing in size when the pulmonary arteries are occluded. Recent reports describe the roentgen findings in postoperative cases of pulmonary embolism without infarction. Significant findings are: (*1*) segmental increased radiability of the lung due to ischemia; (*2*) abrupt termination of the major arterial branches at the site of the embolus; (*3*) relative absence of the vascular pattern in the involved areas; and (*4*) dilatation of the main pulmonary arteries proximal to the embolus. In the case reported with similar roentgenographic findings, cor pulmonale was also present.—*Pulmonary embolism does not necessarily mean pulmonary infarction: A case report, M. E. Woesner, G. A. Gardiner, & W. L. Stilson, Am. J. Roentgenol., March, 1953, 69: 380.*—(*T. H. Noehren*)

Acute Early Pulmonary Embolism.—Of 123 patients who died from pulmonary embolism following surgical operation, trauma, and hemorrhage, 22 died within forty-eight hours of the injury. In all, the diagnosis of pulmonary thrombo-embolism was confirmed by post-mortem examination. In 17 of the 22 cases, pulmonary embolism followed surgical operation; in one, it followed accidental injury; and in 4, it followed hemorrhage. Antecedent shock and hypotension were significantly more common in the patients with early pulmonary thrombo-embolism. The main pulmonary artery was obstructed by a large embolic thrombus in 11 of the 22 patients with early embolism. A statistical comparison of the cases of early and late embolism demonstrated that massive pulmonary embolism was significantly more common when the episode occurred earlier. The probable origin of the embolism was found in 11 of the 22 patients; in 8 the embolus originated in the veins of the lower extremities. Antecedent shock or hypotension was present in 20 of the 22 patients. Antecedent shock or hypotension in patients more than fifty years old may suggest potential candidates for early pulmonary thrombo-embolism.—*Studies in thrombo-embolic diseases: I. Acute early embolism (within forty-eight hours) following surgical operation, trauma and hemorrhage, H. A. Davis, Ann. Surg., March, 1953, 157: 356.*—(*M. J. Small*)

Bilharzial Cor Pulmonale.—Right-sided cardiac hypertrophy and strain following pulmonary endarteritis due to schistosomiasis is now an established entity and is well known in Egypt. Patients with bilharzial cor pulmonale are usually either free or suffer only a mild bilharzial infection of the urinary or intestinal tracts or both. A 29-year-old man with cor pulmonale died after a severe hematemesis. The histologic findings were as follows: "The lungs showed a mild degree of passive congestion and a moderate number of parenchymatous tubercles of fairly recent and healed types. The healed tubercles were extravascular areas of scar tissue, some with calcified ova in the center while more recent ones were formed mainly of collections of lymphocytes around the ova. No ova with their embryo undergoing destruction by giant cells were seen, and no recent tubercles showing mobile histiocytes and eosinophilic leucocytes were present either. These findings are commonly seen in patients with a mild but long-standing bilharzial infestation either of the urinary or intestinal tracts, who have constant emboli to the pulmonary arterioles with *Bilharzia* ova. Angiomas were present in moderate number; they were usually small and of the capillary type. Only a moderate degree of medial hypertrophy of the pulmonary arterioles was seen. The pulmonary artery had a healthy intima but its media was

hypertrophied. The cardiac muscle showed cloudy swelling but no *Bilharzia* ova were seen in sections taken from both ventricles." Similar findings were present in a 32-year-old man with cor pulmonale who died of congestive heart failure.—*Bilharzial cor pulmonale: A clinicopathologic report of two cases, B. Girgis, S. Guirguis, R. Mofawy, & H. El-Katib, Am. Heart J., February, 1953, 45: 190.*—(*G. C. Leiner*)

Urine in Cor Pulmonale.—The urinary findings in 7 cases of congestive failure due to chronic lung disease were investigated. Ordinary congestive failure is characterized by oliguria, high specific gravity, acid reaction, and the presence of albumin, leukocytes, erythrocytes, and casts. With improvement, these features disappear. In the 7 cases investigated, only one showed these features; in that case, there was reason to suspect hypertension as an additional factor. The reason for this difference may lie in the different mechanisms of failure, namely, high cardiac output in cor pulmonale and low output in ordinary failure.—*The urine in seven cases of chronic cor pulmonale, J. J. Segall, Lancet, March 14, 1953, 1: 524.*—(*A. G. Cohen*)

Pulmonary Arteriovenous Fistula.—Hereditary hemorrhagic telangiectasis is a primary vascular disease characterized by a cutaneous, mucosal, and visceral telangiectasis and angiomata, hemorrhages, and a hereditary transmission. The lesions are commonly on the face and on the mucosal surfaces of the lips, tongue, mouth, and gastrointestinal tract. Repeated hemorrhages result in secondary anemia, chronic debility, and, if severe, death. The pulmonary lesions have been called angiomas, varices, aneurysms, cavernous hemangiomas, and arteriovenous fistulas. In many of the original descriptions of pulmonary arteriovenous fistula, the relationship of this pulmonary lesion to hereditary familial telangiectasis either was ignored or was unrecognized; as more cases are recognized and studied, this fundamental relationship is being emphasized. The common subjective symptoms are dyspnea, dizziness, faintness, palpitation, pain in the chest, thick speech, headache, and paresthesias. Characteristic physical findings are cyanosis and clubbing of the fingers and toes. The heart usually is normal on percussion and auscultation, but a pulmonary bruit may be found and may or may not have the continuous sounds of systemic arteriovenous aneurysms. The intensity of the murmur often increases in inspiration and decreases in expiration. Usually there are polycythemia elevated hematocrit, increased total blood volume, and decreased oxygen saturation of the arterial blood. In roentgenographic films of the lungs, there is usually a lobulated opacity with bandlike linear or sinuous trunks connected to the hilus. The fluoroscope may reveal pulsation both in the lesion and in the hilus on the same side. The Valsalva test of deep inspiration followed by forcible expiration against a closed glottis may decrease the shadow's size; Mueller's test of deep expiration followed by forcible inspiration against a closed glottis may increase it. Roentgenologic examination not only aids in diagnosing the syndrome but also in determinating the number of lesions, for the fistulas are more often multiple than single. Pulmonary arteriovenous fistula is most often confused with congenital heart disease and polycythemia. The treatment of the fistula is surgical. Two cases of hereditary hemorrhagic telangiectasis complicated by pulmonary arteriovenous fistula occurred in father and son. In one instance, the complicating lesion was successfully removed by lobectomy.—*Pulmonary arteriovenous fistula associated with hereditary telangiectasis: A report of their occurrence in a father and son, J. R. Tobin & T. C. Wilder, Ann. Int. Med., April, 1953, 38: 852.*—(*T. H. Noehren*)

Bronchogenic Carcinoma Simulating Benign Disease.—Vital statistics reveal a great increase in the incidence of bronchogenic carcinoma. The surgical treatment of this disease has improved considerably but early correct diagnoses are essential for further

progress. Bronchogenic carcinoma may not be recognized when there is a coexistent benign pulmonary disease or when the malignancy simulates a benign pulmonary lesion. In some cases of bronchogenic carcinoma the presenting diagnosis was pulmonary tuberculosis, viral pneumonia, coccidioidomycosis, bronchiectasis, benign lung abscess, cystic bronchiectasis with bronchopleural fistula, pulmonary sarcoma, and mediastinal lymphosarcoma.—*Bronchogenic carcinoma simulating benign pulmonary disease, G. V. Brindley, Jr., Ann. Surg., May, 1953, 137: 616.—(M. J. Small)*

Pulmonary Leiomyosarcoma.—A primary pulmonary leiomyosarcoma, the first reported in a child, measured 7 cm., stretched across the left lower lobe, and invaded the left pulmonary vein and left atrium. It was possible, however, to place a clamp well back on the left atrium, thereby excluding the entire tumor mass. As much of the left atrium as possible was then cut away. It was not possible to determine whether this tumor was primary in the lung or in the bronchus. It was considered to be of pulmonary origin because it was in the left pulmonary vein and because the mass of the tumor was extrabronchial. The child is alive and well without complaints two years after surgery and three years after onset of symptoms.—*Pulmonary leiomyosarcoma in a child, W. P. Killingsworth, G. S. McReynolds, & A. W. Harrison, J. Pediat., April, 1953, 42: 466.—(M. J. Small)*

Bronchial Adenoma.—The bronchial adenoma is a slowly growing epithelial tumor which usually occurs in the main and in the lobe bronchi. It is found almost as frequently in women as in men, commonly in the lower age groups. In patients with recurring pneumonic infiltrations, chronic cough, and hemoptysis, the diagnosis of an adenoma or carcinoma should be considered and bronchoscopy should be done. Bronchoscopic treatment may be undertaken but recurrences are frequent and malignant degeneration is observed in approximately 10 per cent of bronchial adenomas. Hence, resection is advisable either by local excision of the adenoma or by lobectomy or pneumonectomy.—*Klinik und Therapie des Bronchialadenoms, R. H. Jenny, Wien. klin. Wchnschr., February 27, 1953, 65: 169.—(G. C. Leiner)*

Bronchogenic Cysts.—In each of 7 cases of bronchogenic cyst, the clinical, radiologic, and surgical features were those of a solitary cyst. The general pulmonary structure was studied in 3 cases in which lobectomy or total pneumonectomy was performed. In 2 cases there was cystic disease of a minor degree in addition to the large bronchogenic cyst. Microscopically, the associated small lesions had features identical with those of the large cyst. The bronchogenic cyst seems to represent a relatively minor embryonic malformation in which a clinically significant lesion develops during a period of many years. Adequate study may demonstrate multiple foci of cystic disease in a high percentage of cases. In other words, the so-called "solitary" cyst is usually associated with cystic disease of lesser extent in other areas of the lungs. This concept does not apply to those acquired bronchial cysts which have been reported.—*Bronchogenic cysts: A manifestation of congenital polycystic disease of the lungs, E. L. Heller, J. H. Householder, & A. M. Benshoff, Am. J. Clin. Path., February, 1953, 23: 121.—(J. S. Woolley)*

Enterogenic Intrathoracic Cyst.—A two-month-old girl had an infected cyst of the posterior mediastinum. Puncture and withdrawal of approximately 30 ml. of fluid made successful extirpation of an enterogenic cyst possible. Other congenital deformities consisted of kyphosis and scoliosis of the spinal column, rigidity of the neck, and symmetrical muscle spasms of the upper limbs. Two months after operation a respiratory infection, resistant to antibiotic therapy, led to the death of the infant. At autopsy, a large patent ductus arteriosus was found. The cervical spinal column appeared to be amalgamated as in

Klippel-Feil's syndrome.—*An intrathoracic cyst of enterogenic origin in a young infant, F. Kuipers & J. Wieberdink, J. Pediat., May, 1953, 42: 603.—(M. J. Small)*

Intrapleural and Intraperitoneal Radioactive Gold.—A series of 24 patients with pleural effusion or ascites caused by malignant neoplasms were treated by intracavitary injection of colloidal radiogold. Rapid fluid accumulation, necessitating frequent paracenteses, caused the most annoying symptoms. The Au^{198} was in a sterile colloidal preparation containing 10 to 25 millicuries per ml. The most suitable patients were in relatively good condition and had no important symptoms except those related to the fluid. Large masses of neoplastic tissue appeared to be an unfavorable sign. There was no particular discomfort during the administration of radiogold. Approximately twelve to twenty-four hours following treatment, some of the patients had nausea and vomiting. This sometimes lasted two or three days and varied in severity. It was more prominent with intraperitoneal administration than with intrapleural administration. Along with the nausea and vomiting, patients had considerable weakness and malaise, which usually disappeared promptly. Patients given intrapleural radiogold sometimes had pleuritis with a pleural friction rub and some pleural and diaphragmatic pain. Bone marrow depression of slight degree was common. Patients who had favorable results often continued to accumulate fluid for a few weeks after treatment. In some of these patients the fluid became clearer and contained less blood. Another evidence of improvement was the disappearance of malignant cells from the fluid aspirated from these cavities. Of 8 patients who had good control of fluids, 4 had distinct improvement in their general well-being. The results indicated that intracavitary colloidal radiogold injection is of distinct palliative value in selected cases. It produced less radiation sickness than conventional roentgen ray therapy, was simple to administer, and caused minimal unfavorable reactions.—*Intracavitary colloidal radiogold in the treatment of effusions caused by malignant neoplasms, G. A. Andrews, S. W. Root, H. D. Kerman, & R. R. Bigelow, Ann. Surg., March, 1953, 137: 375.—(M. J. Small)*

Traumatic Diaphragmatic Hernia.—Traumatic diaphragmatic hernia may be caused by direct or indirect injury. In a quoted series of 559 cases of diaphragmatic hernia, only 71 were considered to be of traumatic origin. Traumatic diaphragmatic hernia may be recognized at the time of injury, during an interval stage, or after obstruction or strangulation has occurred. In the first phase there is evidence of shock and pain in the upper abdomen; there may be radiation of pain to the shoulders, dyspnea, and cyanosis. Dullness or tympany may be present over the lower thorax, and there may be a shift of mediastinal structures. In phase two, symptoms may be vague, suggesting peptic ulcer, coronary disease, gallbladder disease, or incomplete intestinal obstruction. Phase three is the phase of obstruction or strangulation. The viscera displaced into the thorax become strangulated or obstructed and the symptoms depend entirely upon what organ is affected. A definite diagnosis depends on the examination of the alimentary canal by the use of opaque medium. Although 95 per cent of all traumatic diaphragmatic hernias occur on the left side, the hernia was found on the right side in the present case.—*Herniation of the right diaphragm secondary to trauma, E. C. Strode & C. A. Vance, Ann. Surg., May, 1953, 137: 609.—(M. J. Small)*

Partial Eventration of Right Diaphragm.—The sporadic cases of diaphragmatic eventration, or elevation of the diaphragm without loss of muscle continuity, have been chiefly in adults and the left hemidiaphragm has been most often involved. Only a few cases of right-sided eventration in children have been reported. Partial eventration of the right diaphragm occurred in a five-year-old child. This lesion was successfully treated by thoracotomy and plication of the diaphragm.

Blind diagnostic aspiration is dangerous in such cases and exploratory thoracotomy is preferable to aspiration, pneumothorax, or pneumoperitoneum.—*Partial eventration of the right diaphragm, M. M. Axler & R. L. Rehermann, J. Pediat., March, 1953, 42: 320.*—(*M. J. Small*)

Pigeon Breast and Other Chest Deformities.—Protrusion deformities of the chest of congenital or developmental origin fall into two main groups: the midline protrusions or pigeon breast (pectus carinatum) deformities, and those in which the protrusion is unilateral and parallel to the sternum. In the former group the sternum may be most prominent at its lower end, or it may protrude in an arcuate manner somewhat resembling funnel chest. In the latter group the protrusion follows the line of the costochondral junctions. One explanation of the etiology of protrusion deformities predicates an unequal growth of the ribs and variation in the size and shape of the diaphragm. The symptoms may be vague and concern poor physical development and easy fatigability; but definite dyspnea and chronic cough have been noted. Psychologic disturbances due to the deformity are usually prominent. Surgical procedures can be used to correct these deformities (Author's summary).—*Pigeon breast (pectus carinatum) and other protrusion deformities of the chest of developmental origin, C. W. Lester, Ann. Surg., April, 1953, 137: 482.*—(*M. J. Small*)

Agenesis of the Lung.—The clinical diagnosis of a case of agenesis of the lung was confirmed by bronchoscopic demonstration that the right main bronchus was absent. These malformations have been divided into three classes: (*1*) cases in which no trace of a bronchus or lung is found; (*2*) cases without lung tissue but with some trace of a bronchus; and (*3*) cases in which the main bronchus is incompletely developed and there is marked hypoplasia of one or both lungs. The present case was true agenesis with no trace of the lung, bronchus, or vascular supply on the right side. A clinical diagnosis can usually be suspected on the basis of the physical findings, the roentgenographic and fluoroscopic findings. Displacement of the mediastinum and heart toward the affected side is suggestive, especially if anomalies of the spine and the ribs are also present. Bronchoscopic examination, with bronchography and angiocardiography, may be necessary in some cases to establish the diagnosis. Because these procedures are dangerous, the latter should be performed only after due consideration of each case and only by experienced bronchoscopists.—*Agenesis of the lung: Report of a case, with a review of all previously reported cases, A. Oyamada, B. M. Gasul, & P. H. Holinger, A. M. A. Am. J. Dis. Child., February, 1953, 85: 182.*—(*M. J. Small*)

Aberrant Lung Lobe.—A true aberrant pulmonary lobe is a compact unit of lung tissue connected with the respiratory tract, which has developed normally in other respects. The aberrant lobe is dark gray-red, conical or discoid, and located near the diaphragm. Of the 40 known examples, including the present one, 32 have been above the diaphragm, 8 below it. Blood is supplied by the systemic circulation, usually by the aorta. An aberrant lobe is more common on the left than on the right side. It is frequently accompanied by a diaphragmatic hernia. Histologically, it consists of pulmonary tissue which is more or less mature and often shows cystic degeneration. The clinical diagnosis is very difficult since these lobes are too small to cause symptoms. A twenty-one-year-old woman had had a congenital hernia diagnosed at the age of ten. At operation a *relaxatio diaphragmatis circumscripta* was found; atop this was an aberrant lung lobe, measuring 6 by 6 cm. Histologically, this was a rudimentary lobe which contained alveoli, bronchi, bronchiectases, and lymphocytic infiltrations, as well as cystic degeneration. This case is the second successfully operated upon.—*Ueber einen Fall von echtem aberrantem Lungenlappen, W. Bruck, Wien. klin. Wchnschr., April 17, 1953, 65: 304.*—(*G. C. Leiner*)

Congenital Lung Anomalies.—The congenital anomalies of the lung may be classified as follows: (*A*) Deficiency malformations (*Mangelmissbildungen*); (*1*) aplasia, (*a*) of both lungs and (*b*) of one lung; (*2*) cystic cavity formations in the lung, (*a*) honeycombed lung, (*b*) central, solitary, cystic cavities, and (*c*) peripheral cysts; (*3*) congenital bronchiectasis. (*B*) Excess malformations; (*1*) true aberrant lobes, (*2*) intrapulmonary cystic cavities with proper blood supply from the aorta, (*3*) ciliated epithelial cysts, and (*4*) congenital tumor-like malformations. (*C*) Malformations of the external appearance; (*1*) dystopies of the bronchial tree, and (*2*) anomalies of the lobes.—*Ueber die Missbildungen der menschlichen Lunge und die Möglichkeit ihrer chirurgischen Behandlung, H. Bruck, Wien. klin. Wchnschr., March 27, 1953, 65: 241.*—(*G. C. Leiner*)

Loculated Azygos Fissure Effusion.—Loculated effusion in the azygos fissure occurred in a patient with cardiac failure. Interlobar effusions are not uncommon in cardiac failure. Most frequently they are located in the right lesser fissure, rarely in the azygos fissure.—*Loculated azygos fissure effusion in cardiac failure, R. L. Friedman, Ann. Int. Med., March, 1953, 38: 582.*—(*T. H. Noehren*)

Chemotherapy of Empyema.—Between 1948 and 1951, 34 of 124 cases of pleural empyema were treated conservatively. There were 29 male and 5 female patients, between one and one-half and seventy-four years of age. Three forms of treatment were used: (*1*) intrapleural chemotherapy without pleural drainage, (*2*) intrapleural chemotherapy with Bülau drainage, and (*3*) Bülau drainage alone. The results showed that local antibacterial treatment should be started early and the pleural cavity emptied as completely as possible. The sensitivity of the bacteria to antibiotics and sulfonamides should be tested repeatedly. Drainage, eventually by suction, is indicated in serious cases only. Tests for bronchopleural fistulas should be done. Chemotherapy should be stopped only after several bacteriologic examinations have been negative.—*Ueber Ergebnisse konservativ behandelter Pleuraempyeme, E. Strahberger, Wien. klin. Wchnschr., April 10, 1953, 65: 277.*—(*G. C. Leiner*)

ANTIMICROBIAL THERAPY

Isoniazid for Renal Tuberculosis.—Resected kidneys were obtained from 9 patients who had received isoniazid alone. The period of treatment before operation was less than one month in 4 cases, six weeks in 2, and three months in one. The specimens contained all degrees of tuberculous lesions from very small ulcers at the tip of a calyx to extensive lesions involving all of the calyces. Grossly, the lesions showed a degree of congestion most unusual in untreated tuberculous lesions. In addition, frank hemorrhages were found either in the cavity in the cortex and under the capsule or under the mucosa of the calyx or pelvis. Microscopically, there was absorption of recent caseation, vascularization of the edges of the lesions, inactivation of epithelioid cells, and complete lack of fibrosis. In open lesions, the optimal effect appeared after one month of treatment; there was some retrogression after three months of treatment. In the more chronic lesions, the effect of treatment was not manifested until after one month. These changes indicate an extraordinary beneficial effect of isoniazid, not only on acute lesions, but also on chronic lesions.—*Effect of isoniazid on tuberculous lesions of the kidneys, J. C. Dick, Lancet, April 25, 1953, 1: 808.*—(*A. G. Cohen*)

Resistance to Isoniazid.—The sensitivity of *M. tuberculosis* to isoniazid before and during the treatment of 29 patients with pulmonary tuberculosis with cavitation was determined on three occasions, each time with two different techniques. At the time of the first sensitivity study, 5 patients had already been treated with isoniazid for two months or longer; the remaining 24 had never received drugs of the isoniazid group. After this initial test, the first 5 patients continued their treatment and the other 24 patients

were started on therapy with isoniazid, which was given alone in 6 cases, with *p*-aminosalicylic acid in 9, and with streptomycin in 9 other cases. New sensitivity studies were done one and three months after the initial determination. There was practically no increase in the degree of resistance of *M. tuberculosis* to isoniazid. Furthermore, the levels of sensitivity were all within the limits of the therapeutic plasma concentrations of the drug. The slight variations in the initial sensitivity levels which were found among the 29 patients had no influence on the apparent therapeutic efficacy of isoniazid (Author's summary).—*Sensibilité à l'hydrazide de l'acide isonicotinique des bacilles de Koch isolés de l'expectoration de 29 malades avant et pendant traitement parallèle clinique, J. Letacon, P. Dubreuil, J. Poulet, & J. Fourchon, Presse méd., March, 1953, 61: 324.—(V. Leites)*

Resistance to Isoniazid.—In 2 cases of pulmonary tuberculosis, clinical resistance to isoniazid developed following forty and seventy days of treatment, respectively. The tubercle bacilli isolated from these cases grew in a medium containing 100 γ of drug per ml.—*Resistência do bacilo de Koch á hidrazina do ácido nicotínico, J. Rosemberg, R. Brandi, & L. Nogueira Carrijo, Rev. brasil. tuberc., January–February, 1953, 21: 63.—(A. A. Moll)*

Antituberculous Activity of Substituted Thioureas.—More than 350 thioureas were tested for their antituberculous activity. Certain di-substituted thioureas demonstrated considerable protective and therapeutic activities in tuberculous mice and guinea pigs and also possessed strong antifungal activity. Little relationship was found between *in vivo* and *in vitro* tuberculostatic activities; a number of compounds were more active *in vivo* than *in vitro*, suggesting the possibility of a metabolic transformation into more active products. On guinea pigs, some substituted thioureas were more active than *p*-aminosalicylic acid or streptomycin and similar to isoniazid. No strains resistant to thioureas have been found so far.—*Antituberculous activity of substituted thioureas, R. L. Mayer, P. C. Eisman, & E. A. Konopka, Proc. Soc. Exper. Biol. & Med., April, 1953, 82: 769.—(E. Soto Figueroa)*

Therapeutic Target in Tuberculosis.—The modern chemotherapeutic agents have created new problems in the treatment of tuberculosis; for example, the question of home treatment *versus* sanatorium care. Chemotherapy has complicated treatment in part because marked therapeutic effects apparently go hand in hand with the earlier development of drug resistance. It is questionable whether new and better chemotherapeutic agents will solve the problems of drug resistance; combined therapy and alternating short periods of treatment with different agents are currently recommended to delay the development of resistance. Improvement in subjective symptoms, reduced fever, weight gain, decreased sedimentation rate, decreased cough and expectoration, and decreased bacillary content of sputum are important in evaluating the results of therapy but are not the true therapeutic target. Even the disappearance of tubercle bacilli from the sputum is a questionable criteria of efficacy since this is often seen in patients with persistent cavities. The therapeutic target is reached when both cavity closure and negative bacteriologic studies are obtained. This increases the importance of tomography for the detection of remaining cavitation.—*Die Kriterien des Therapieerfolges bei der Lungentuberkulose, F. Rotach, Schweiz. med. Wchnschr., February 14, 1953, No. 7: 148.—(E. Dunner)*

Treatment of Minimal Tuberculosis.—Of 80 cases of early minimal tuberculosis observed for three years, 20 were treated with daily streptomycin, 30 with pneumothorax, and 30 with rest alone. All of the patients were women fifteen to forty years old. Rest consisted of staying in bed sixteen hours of the twenty-four, fourteen hours of these at complete inactivity. This regimen was followed by a post-cure period, the total treatment

requiring at least one year. Patients given streptomycin were treated between 1947 and 1949, the others from 1940 to 1947. Among those given streptomycin in addition to bed rest, there were 18 failures (35 per cent). Two of these showed no improvement in the first months and were given pneumothorax; 5 patients relapsed one to three years later. One patient's lesion increased during treatment and regressed after it was discontinued. Among the 30 patients treated with rest alone, there were 12 failures (40 per cent). One of these died of hemoptysis early in treatment. All 4 patients who received only six instead of the prescribed minimum of twelve months' treatment relapsed. Among the 30 patients receiving pneumothorax, there were only 2 (6 per cent) failures. One of these showed local spread three years after re-expansion of a pneumothorax maintained for five years. If the follow-up period is reduced to three years, to correspond with the streptomycin-treated cases, it leaves only one failure (3 per cent). Of the factors other than the mode of treatment which might influence the results, age was of some importance in that the younger the person the greater was the chance of failure. Neither the bacillary content of sputum nor the extent of the lesion had much influence. The radiologic character of the shadow was of some prognostic importance; discrete soft shadows, even when extensive, tended to resolve better than denser ones. Maintaining a long period of bed rest in association with streptomycin therapy is most important.—*Parallèle entre les résultats obtenus par les divers traitements médicaux opposés aux infiltrats nébuleux saisis a leur phase initiale, A. Dufourt, C. Ollagnier, A. Depierre, & H. Phelip, Poumon, January, 1953,* **9:** 1.—(*F. S. Lansdown*)

Chemotherapy in Preparation for Surgery.—From January, 1951, to June, 1952, 90 tuberculous patients were prepared for surgical intervention with streptomycin and *p*-aminosalicylic acid. One group of 38 patients received streptomycin daily and another group of 38 were treated semi-weekly. In each group some patients received pneumoperitoneum in addition. The results in the two groups were identical. Patients whose lesions were expected to regress were treated for two months. Patients who had already improved on sanatorial care were given chemotherapy for approximately one month preoperatively. There were only 2 tuberculous complications among 78 operations, namely, thoracoplasties, extrapleural pneumothoraces, Lucite plombages, and resections. No alterations in the bacillary streptomycin sensitivity occurred among patients who had never received the drug. On the other hand, resistant bacilli appeared early in those who had previously received it. A period of rest following operation is important. Several relapses have already been encountered among patients with excellent early results who refused further sanatorium care.—*La streptomycine en injections quotidiennes et en injections espacées associée au P.A.S. dans la préparation aux interventions chirurgicales pour tuberculose pulmonaire, P. Oudet, F. Koebele, J.-P. Hutt, & P. Merklen, Poumon, January, 1953,* **9:** 13.—(*F. S. Lansdown*)

Aureomycin with Penicillin for Pneumonia.—The response of 25 patients with pneumococcic pneumonia to penicillin and aureomycin was compared with that of a similar group treated with penicillin alone. The patients were in general aged and debilitated, and many had severe alcoholism. Positive blood cultures were obtained for 17 patients (34 per cent), and there were 6 deaths (12 per cent), 3 in each group. From the standpoint of symptomatic improvement, temperature response, disappearance of pulmonary infiltrations, and length of hospitalization, the results were essentially the same in the two groups; i.e., there was no evidence of antibiotic antagonism. This phenomenon is probably of clinical importance only in certain diseases, such as pneumococci meningitis. Following initial improvement, there was a recurrence of fever, cough, and sputum in 6 of the 50 patients, and *Micrococcus aureus* was recovered from the sputum in pure culture.

In two of these patients pulmonary cavitation developed, and one patient died (Authors' summary).—*Lack of interference of aureomycin with penicillin in treatment of pneumococcic pneumonia, J. J. Ahern & W. M. M. Kirby, A. M. A. Arch. Int. Med., February, 1953, 91: 197.*—(*G. C. Leiner*)

Actidione for Disseminated Coccidioidomycosis.—A severe, disseminated case of coccidioidomycosis in an infant was completely cured with Actidione, an antibiotic derived from *Streptomyces griseus*. Coccidioidal osseous involvement with draining sinuses and pulmonary involvement was proved by positive cultures for *Coccidioides immitis*. Therapy was begun with Actidione when the infant was ten months old and was continued for one year. The child died at four years and eight months of age. A post-mortem examination revealed the cause of death to be a sympathicoblastoma of the adrenal gland with metastasis to the brain; there was no evidence roentgenologically, histologically, or culturally of any residual coccidioidal lesions. The same drug was tried clinically for two years with poor results in many other cases of disseminated coccidioidomycosis. This case gives encouragement to the further search for a less toxic drug.—*A proven case of a cured disseminated coccidioidomycosis, R. Cohen & M. A. Gifford, Arch. Pediat., March, 1953, 70: 81.*—(*M. J. Small*)

Pleuropneumonia-like Organisms.—Twenty strains of pleuropneumonia-like organisms were tested for their sensitivity to penicillin, streptomycin, dihydrostreptomycin, aureomycin, chloramphenicol, and terramycin. Penicillin was not inhibitory in a concentration of 800 γ per ml. Dihydrostreptomycin was less effective than streptomycin. Sensitivity to aureomycin and chloramphenicol was significantly higher than reported by other workers, requiring a minimum inhibitory concentration of 0.32 to 1.25 and 2.5 to 10 γ per ml., respectively. Prolonged incubation in other studies may have allowed the aureomycin or chloramphenicol to deteriorate and this may account for the apparent lower sensitivity to the drugs. Contrary to previous reports, noninhibitory concentrations of aureomycin and chloramphenicol did not enhance growth. The most effective drug was terramycin, which inhibited growth in concentrations of 0.16 to 0.63 γ per ml.—*The susceptibility of pleuropneumonia-like organisms to the in vitro action of some antibiotics, B. Melen, Acta path. et microbiol. Scandinav., 1952, 30: 98.*—(*H. G. Turner*)

LABORATORY STUDIES

Antimycobacterial Effect of Various Amines.—Under certain conditions the organic base spermine exerts *in vitro* a powerful antimycobacterial action. The effects of various biologic and synthetic amines structurally similar to spermine were tested by adding the free amines or their salts to a modified Dubos liquid medium which contained no Tween or albumin. BCG organisms were introduced into each tube from a liquid suspension containing bovine plasma fraction and glucose. Thus, in each tube was now a small amount of albumin and glucose in addition to the medium already present. Although spermine or spermidine in very high dilution inhibited the growth of BCG, various related amino compounds, including isolated portions of the spermine molecule and the product of its chemical degradation, did not exhibit similar activity.—*The antimycobacterial activity of various amines related to spermine in chemical structure, J. G. Hirsch, J. Exper. Med., March 1, 1953, 97: 323.*—(*J. S. Woolley*)

Spermine Inhibition of Mycobacteria.—Although spermine and spermidine in many instances inhibit the growth of tubercle bacilli, they generally have no effect on *Mycobacteria* or on many nonacid-fast organisms. Spermine and spermidine inhibit the growth of tubercle bacilli only if a certain tissue substance is present in the medium. This activating substance occurs as a contaminant of the albumin in commercial bovine plasma fraction V, which ordinarily

is added to culture media. When certain whole sera are substituted for fraction V, growth is no longer inhibited; inhibitory activity is restored by adding bovine albumin to the media containing the whole serum. An attempt was made to isolate this activating substance, which was found in whole bovine and sheep serum and in aqueous extracts of the guinea pig kidney but not in whole human, guinea pig, or rabbit serum. The activating substance appeared to be an alpha globulin, an enzyme which acts on spermine. Some product of an enzymatic reaction between this substance and spermine exerts a toxic effect on mammalian tubercle bacilli, which seem to be peculiarly susceptible. The antibacterial action usually appears only after two or three days of incubation, presumably because spermine is slowly altered to form a bactericidal substance.—*The essential participation of an enzyme in the inhibition of growth of tubercle bacilli by spermine, J. G. Hirsch, J. Exper. Med., March 1, 1953, 97: 327.—(J. S. Woolley)*

Spermine Oxidase.—Spermine and spermidine act as antimycobacterial agents only in the presence of an enzyme which has been found in bovine and sheep serum and in aqueous extracts of the guinea pig kidney. This enzyme differs from other amine oxidases in several regards and especially in its substrate specificity; only spermine and the closely related compound, spermidine, serve as substrates for the enzyme in sheep serum. For this reason the enzyme has been named spermine oxidase. This oxidase is active in fluids of various ionic strength and buffer composition between pH 6.0 and pH 8.0 with an optimal rate near neutrality. Under certain conditions, the rate of oxygen consumption during the initial phase of the reaction is independent of the substrate concentration. During the latter phase of the enzymatic reaction, the rate diminishes, apparently due to the altered kinetics at low substrate concentrations or to competitive inhibition by a product of the reaction. Carbonyl reagents almost completely block the action of spermine oxidase, while certain amines and the cyanide ion bring about partial inhibition. Thiol reagents and sequestering compounds do not alter the course of the oxidative process. In the presence of low concentrations of mercuric chloride, the sheep serum-spermine system consumes approximately twice as much oxygen as controls containing no mercuric ion. The mechanism by which the mercuric ion stimulates additional oxygen uptake is obscure.—*Spermine oxidase: An amine oxidase with specificity for spermine and spermidine, J. G. Hirsch, J. Exper. Med., March 1, 1953, 97: 345.—(J. S. Woolley)*

Effect of Environment on Tubercle Bacilli in Vitro.—The disappearance of tubercle bacilli from such lesions as closed cavities and cold abcesses is believed to result from low oxygen tension, the concentration of carbon dioxide, and the action of organic acids produced by anaerobic metabolism. The effect of other substances released from the tissues by autolytic processes must also be considered. Experiments were designed to test the effect on the viability of tubercle bacilli of some of the factors presumed to operate in the tuberculous lesion, using 5 strains of virulent and avirulent tubercle bacilli. These strains were grown on several modifications of Tween-albumin broth; the tubes were then exposed to various gasses either directly or after the addition of sodium lactate or alanine. The viable bacilli remaining were counted by plating them on oleic-acid–albumin agar. Tubercle bacilli died much more rapidly under anaerobic than under aerobic conditions. In the presence of oxygen, carbon dioxide and certain metabolites such as lactate increased the death rate. When the bacilli died under certain anaerobic conditions, they lost their ability to take the acid-fast stain and showed progressive cellular disintegration. Thus, the defense mechanisms against tuberculous infection operate, not only through the ordinary immunologic reactions, but also by creating a physicochemical environment which interferes with

the multiplication and survival of tubercle bacilli. The inflammatory process is modified by allergy, by hormonal control, and by anatomic accidents, such as communication with a bronchus or blood vessel. The peculiarities of the process determine the physicochemical characteristics of each tuberculous lesion and, hence, the environmental factors which affect the multiplication and survival of the bacilli. In this sense, local immunity may differ from the general immunologic state of the body and yet be influenced by it. This may account for the fact that the bacilli can thrive and produce progressive disease in one part of an organ, while being held in check in another area, even in the same organ.—*Effect of the composition of the gaseous and aqueous environments on the survival of tubercle bacilli in vitro, R. J. Dubos, J. Exper. Med., March 1, 1953, 97: 357.—(J. S. Woolley)*

Tubercle Bacilli in Milk.—The use of guinea pigs, Dubos liquid and solid media, and other media has been studied in the isolation of tubercle bacilli from milk. The main problem was the control of contaminants found in bulk milk. Trisodium phosphate (10 per cent) was the most satisfactory chemical for this purpose, but this agent and 4 per cent sodium hydroxide had a significantly lethal effect on bovine tubercle bacilli. These two chemicals were suitable only when specimens after treatment were cultured on Dubos solid medium containing 100 units of penicillin per ml. Oxalic acid (5 per cent) was of little value since it did not control satisfactorily the molds present in the milk samples. Direct microscopy and cultural examination on Dubos penicillin agar were carried out on 312 samples of bulk milk from groups of cows. Thirty had been shown by guinea pig inoculation at the Veterinary Investigation Centre, Cambridge, to contain tubercle bacilli. Of these, 16 (55.3 per cent) were positive on culture and 10 (33.3 per cent) on direct microscopic examination. Other acid-fast bacilli were observed during the direct microscopic examination of 26 (8.3 per cent) milk samples which were negative by guinea pig inoculation and culture (Author's summary).—*The demonstration of tubercle bacilli in milk, H. Williams Smith, J. Path. & Bact., 1953, 65: 67.—(H. J. Henderson)*

Unidentified Acid-Fast Bacillus.—An unidentified acid-fast bacillus was isolated from the sputum of a patient. This organism was highly pathogenic for mice but nonpathogenic for guinea pigs, rabbits, fowl, and frogs. The name of *Mycobacterium sp.*, strain Glascow, is suggested.—*An unidentified acid-fast bacillus (Mycobacterium sp., strain Glascow) found in human sputum and lung lesions, I. Lominski & E. M. Harper, 1953, 65: 253.—(H. J. Henderson)*

Stefanski's Bacilli.—Thirty rats infected by the subcutaneous route with 1.0 ml. of a suspension of Stefanski's bacilli were treated twenty-four to seventy-two hours after inoculation with 0.75 to 1.0 mg. of isoniazid by mouth daily for six to seven months. The treated animals showed no lesions clinically. Histologic examination revealed minimal alterations at the site of inoculation and in the corresponding lymph node which contained deteriorated bacilli. Fifteen controls infected at the same time and with the same dose developed the classical disease of early lesions at the site of infection and massive lymphatic dissemination. No antibiotic or chemical agent had been able heretofore to inhibit the formation of a lesion with subsequent lymphatic dissemination of bacilli following experimental infection with Stefanski's bacilli (Author's summary).—*Action de l'hydrazide de l'acide isonicotinique sur le rat infecté par le bacille de Stefanski, R. Chaussignaud, M. Viette, & O. Krug, Ann. Inst. Pasteur, February, 1953, 83: 433.—(V. Leites)*

Properties of Vole Bacilli.—Both in cultures and in smears, Wells' vole acid-fast bacilli were as granular as *M. leprae*, *M. tuberculosis*, and Stefanski's bacilli. They also had a degree of fluorescence similar to

that of other virulent tuberculosis organisms. Their cytochemical virulence reaction was fully as strong as that given by BCG, *M. tuberculosis*, human strain 512, Dufray's bovine strain, and Vallée's bacilli. White mice inoculated with vole bacilli developed tuberculosis within twenty-two days and had musculo-cutaneous lesions similar to those reported in voles with naturally acquired tuberculosis.—*Estudos experimentais com "vole bacillus" (Mycobacterium tuberculosis var. muris) no Instituto Oswaldo Cruz, H. C. de Souza Araujo, Rev. brasil. med., January, 1953, 10: 1.*—*(A. A. Moll)*

Bronchial Transplantation in the Dog.—In the dog, bronchial resections with direct anastomosis can be done safely. Bronchial transplantation with or without bronchial resection can be made to a new site on the trachea or contralateral bronchus. The distance and direction of the transplantation is limited by the length of the pulmonary veins and, in addition, on the left side by the aortic arch. Resection of the carina, the carina and stem bronchi, carina and one lung, followed by reconstruction, can be done as a one-stage procedure. The mortality is not prohibitive. Long tracheal defects can be bridged with immediate success by tantalum mesh gauze alone. A narrowed lumen eventually results due to posterior indentation of the "graft" in juxtaposition to the esophagus. Respiratory and ventilatory function of pulmonic tissue distal to a resection and reconstruction is apparently normal (Authors' summary).—*An experimental evaluation in the dog of bronchial transplantation, bronchial, tracheal and tracheobronchial resection with reconstruction, L. B. Kiriluk & K. A. Merendino, Ann. Surg., April, 1953, 137: 490.*—*(M. J. Small)*

Pulmonary Damage by Oxygen.—Hypophysectomized and nonhypophysectomized rats were constantly exposed to oxygen in concentrations of 90 to 98 per cent at normal atmospheric pressure in a chamber from which carbon dioxide was continuously absorbed. The nonhypophysectomized animals became dyspneic and lethargic within twenty hours of exposure and rapidly deteriorated. Several died within forty-five hours and all died or were killed in a terminal state within seventy hours of exposure. The thoraces were filled with clear, watery, bloodless fluid which clotted firmly on standing. The lungs were deep brownish-purple, rubbery, devoid of air, and sank in the fixing solution. The massive hydrothorax may explain the decreased vital capacity commonly seen during exposure to oxygen at normal atmospheric pressure. In contrast to these findings, none of the hypophysectomized animals died and all were active but dyspneic when killed after seventy hours of exposure. The thoraces contained little free fluid. The lungs appeared essentially normal and all contained air. These results confirm earlier findings that hypophysectomy protects against the pulmonary damage inflicted by oxygen. The operation eliminates or diminishes those substances which are released in the normal animal and which make pulmonary tissue, particularly the vascular bed, more susceptible to injury by oxygen in high concentrations. Corticotropin and cortical hormones, among them cortisone, constitute important parts of this augmentatory mechanism but are not essential to the precipitation of injury by oxygen. (Authors' summary).—*Hypophyseal and adrenocortical factors in pulmonary damage induced by oxygen at atmospheric pressure, J. W. Bean & C. W. Smith, Am. J. Physiol., January, 1953, 172: 169.*—*(G. C. Leiner)*

Pulmonary Blood Flow.—Pulmonary arterial and venous pressures were obtained from anesthetized dogs by the technique of cardiac catheterization. Blood flow was measured by the Fick method. The calculated resistance to the flow through the pulmonary circuit was determined while the animals were breathing 8, 15, 21, and 30 per cent oxygen in nitrogen or a mixture containing 5 per cent carbon dioxide, 25 per cent oxygen, and 70 per cent nitrogen. It was found that the

resistance increased 25 and 48 per cent as the inspired oxygen tension decreased from 21 to 15 and 8 per cent, respectively, but did not change when the carbon dioxide tension of the inspired air was raised. An attempt was made to relate these changes to actual alterations in the relative caliber of the pulmonary vessels. It appears that these changes in resistance are produced by actual vasomotion. Three dogs subjected to a two-stage thoracic sympathectomy failed to show an increased resistance postoperatively when breathing 8 per cent oxygen-nitrogen mixture (Authors' summary).—*Effect of O_2 and CO_2 tensions upon the resistance of pulmonary blood vessels, R. C. Stroud & H. Rahn, Am. J. Physiol., January, 1953, 172: 211.*—(*G. C. Leiner*)

Pulmonary Uptake of Fluid.—Radioactive iodine (I^{131}) in the form of sodium iodide or radiosodium (Na^{24}) in the form of sodium chloride are convenient labels for estimating the uptake of fluid introduced by tracheal catheter into the lungs of dogs. Physiologic saline solution introduced into the lung in volumes of 1.0 to 6.0 ml. per kg. of body weight disappears with a mean half-time of 15.5 ± 0.8 minutes (standard deviation 4.4), while distilled water disappears with a half-time of 3.8 ± 0.4 minutes (standard deviation 1.4). These mean half-times differ by a factor of 4. There is marked variability in the half-time from dog to dog and in the same dog on different days. This does not vary in any consistent manner with the state of hydration, venous pressure, respiration rate, liquid or atomized administration, hematocrit value, or plasma protein concentration. When repeated determinations of uptake either of water or saline are made on the same dog the same day, quite reproducible half-times are obtained. This would indicate that determination of the half-time for uptake of water or saline constitutes a measure of the osmotic-oncotic pressure gradients between alveolus and capillary which exist as of the moment (Authors' summary).—*Rate of uptake of fluid from lung measured with radioisotopes: Comparison of rapid rate for water with slower rate for saline, G. Qualls, H. J. Curtis, & G. R. Meneely, Am. J. Physiol., January, 1953, 172: 221.*—(*G. C. Leiner*)

Hypothermia for Intracardiac Surgery.—In monkeys at a body temperature of 16° to 19°C. it has been possible to exclude the heart from the circulation and open it for fifteen to twenty-four minutes with survival in 12 of 13 experiments. In groundhogs at a body temperature of 3° to 5°C., the heart has been excluded and opened for periods of one to two hours with survival in 5 of 6 experiments. Prolonged interruption of the circulation and exclusion of the heart with survival is possible at low body temperatures. The length of time that a heart may be excluded from the circulation appears to be increased as the body temperature is reduced. Age appears to be an important factor in cold tolerance. A greater knowledge of hibernation may yield useful information on this problem (Authors' summary).—*Further experiences with hypothermia for intracardiac surgery in monkeys and groundhogs, W. G. Bigelow & J. E. McBirnie, Ann. Surg., March, 1953, 137: 361.*—(*M. J. Small*)

PUBLIC HEALTH AND EPIDEMIOLOGY

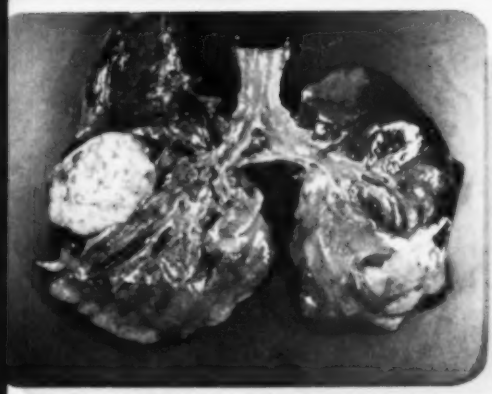
Tuberculosis in Pregnancy.—It was decided to look for unsuspected tuberculosis in mothers attending an antenatal clinic in a district where tuberculosis is common. Known tuberculosis cases were excluded from the series. A total of 541 patients received roentgenographic examination of the chest. Evidence of tuberculosis was found in 29 (5.3 per cent). An additional 4 per cent showed calcified lymph nodes. Of the 29 tuberculosis cases, 12 showed only calcified lesions; in the other cases, the lesions were either active or fibrotic. In 4 cases, the lesions were definitely fibrotic; and in one, suspicious. Following delivery, re-examination showed no change in the 4 active cases; 2 of the inactive cases became active.—*Routine X-ray examination*

of the chest at an antenatal clinic, A. Freeth, Lancet, February 7, 1953, 1: 287.—(A. G. Cohen)

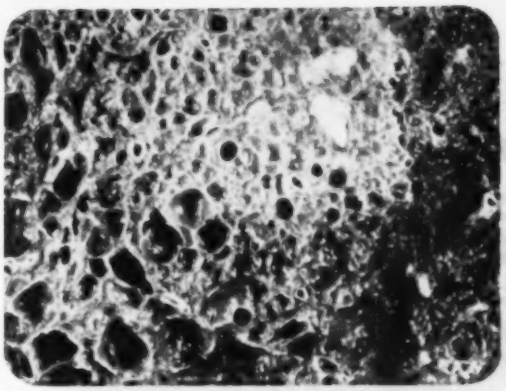
Mortality Decrease in Tuberculosis Hospitals.—The death rate is decreasing among tuberculous patients in a Rio de Janeiro hospital. Inmates now live longer and remain longer under care. Approximately a decade ago, it was common to see new patients die within a month, a week, or even hours after admission. Of 183 patients in January, 1952, 40.9 per cent had been hospitalized at least thirteen months, most of them having been there several years. In 1940, the highest death rate was in the 11- to 20-year age group; in 1951, in the 21- to 30-year group. In 1940, 72.8 per cent of the deaths occurred during the first six months after arrival; in 1951, only 49.3 per cent. This change has brought a new problem of how best to handle these older patients.—*Diminuição da letalidade tuberculosa nos hospitais de tuberculose, A. de Paula & R. Simonard, Rev. brasil. tuberc., January–February, 1953, 21: 3.—(A. A. Moll)*

Beryllosis Complicated by Tuberculosis.—A case of chronic granulomatosis of the lungs due to beryllium was complicated by pulmonary tuberculosis. A seemingly insignificant exposure to beryllium oxide dust eight years before death produced grave manifestations; the etiology was still demonstrable by chemical detection of the toxic agent after necropsy. The early history and clinical course of this case was characteristic of beryllium granulomatosis. Later the unusual intercurrent tuberculous infection adversely affected the course. Corticotropin produced a definite clinical remission, with defervescence and improvement of the objective as well as the subjective manifestations of pulmonary disease. Until the spread of tuberculosis vitiated its beneficial effects, corticotropin improved respiratory function, weight, and strength. Toxic manifestations were not sufficiently marked to warrant discontinuing the treatment. The pathologic findings demonstrated the essential similarity of tissue response to the two etiologic agents, beryllium and tubercle bacilli.—*Beryllium granulomatosis complicated by tuberculosis: Report of a case treated with ACTH, R. L. Dorson, J. C. Weaver, & L. Lewis, Ann. Int. Med., February, 1953, 38: 312.—(T. H. Noehren)*

Demonstration of BCG Potency.—In addition to the standard tuberculin tests, Mitsuda's lepromin test is of value in checking the potency of BCG and its absorption in the human body. Lepromin is injected on the same day that BCG is given. During the following days, the skin is examined to detect the onset of the reaction. Tuberculin tests are then made. Young children, preferably newborn and infants, who have been isolated from birth should be used. With this method, BCG was found to be potent after ten days in the refrigerator at 4°C. When given orally, it caused a positive lepromin reaction within sixty days. Results were similar with Rosenthal's multipuncture technique. After BCG had been in the refrigerator for forty-five days, the lepromin test seldom became positive and tuberculin allergy was absent. With heat-killed BCG, results were even more disappointing. The use of the tetrazole reduction to test the potency of BCG is still questionable. There is an unexplained interval between the time when tetrazole is no longer reduced and the time when the bacilli die. Tuberculin and lepromin tests demonstrated that the usual dosage of 0.1 gm. of 10- to 15-day-old BCG is usually sufficient. However, when only 25-day-old BCG is available, the amount should be 0.2 gm.—*Contribuição ao estudo sôbre a vitalidade do B.C.G. (Nota prévia), J. Rosemberg, N. Souza Campos, J. N. Aun, & R. Brandi, Rev. brasil. tuberc. January–February, 1953, 21: 11.—(A. A. Moll)*



Bronchogenic Carcinoma



Pulmonary Emphysema

To get the most out of slides

. . . right at your desk . . . in bright light

IF YOU TEACH—must constantly confer with students and associates on problems of identification and diagnosis . . .

If you have a specialty which involves before-and-after changes—for example, plastic surgery—or skin diseases . . .

If you have large collections of 2 x 2-inch slides, are constantly adding—eliminating—substituting . . .

Whatever your reason, if you show 2 x 2-inch slides to small groups, you need a Kodaslide Table Viewer, Model A.

It embodies projector, black Kodak DAY-VIEW Screen and slide changer in one compact, lightweight unit. Ideally suited for showings at desk. Gives almost 5x magnification with full justice to the color and detail of transparencies. Finger-touch focusing. Plunger type slide changer accepts 75 cardboard or 30 double-glass slides. Price $97.50, subject to change without notice.

For further information see your photographic dealer or write:

EASTMAN KODAK COMPANY
Medical Division, Rochester 4, New York

. . . ving medical progress through Photography and Radiography

Kodak
TRADE-MARK

Why Over 3,500 TB Case-Finding Projects Annually Use

POWERS X-RAY SERVICE

- **POWERS SERVICE IS COMPLETE!** Powers relieves project sponsors of *all* technical problems. Our experienced technicians work to the sponsor's schedule, with units able to take as many as 200 chest x-rays an hour. We deliver fully processed x-rays, with a viewer, to sponsor's roentgenologist.
- **LOWER IN COST!** The large volume of x-rays Powers handles nationally enables us to cut overhead costs to a minimum for each individual project.
- **EFFICIENT!** Our 20 years of experience in chest x-ray surveys from Maine to Texas have taught us to do the job quickly and effectively under many diverse conditions.
- **FLEXIBLE!** According to the sponsor's requirements, Powers offers either the full-size roll paper method or the 70 mm photofluorographic method – and operates either portable units or mobile units with generators.

Reg. T.M. POWERS X-RAY PRODUCTS

Our technical advisory service is available without obligation. Write before you plan a TB Case-Finding Project!

POWERS X-RAY PRODUCTS, INC.

Group Radiography

GLEN COVE, LONG ISLAND, N. Y.

POSITIONS AVAILABLE AND WANTED

RATE $3.50 per insertion for 25 words or less; additional words—15 cents each. Bold face semi-display $5.00 per insertion for 25 words or less; additional words—20 cents each. Box number—75 cents extra. Employment Bureaus—$10.00 per column inch. Remittance should accompany copy and be sent to: American Review of Tuberculosis, 280 Madison Ave., New York 16, N.Y.

POSITIONS AVAILABLE

WANTED: Well-qualified Medical Superintendent in Westmount Tuberculosis Sanatorium, Warren County, Glens Falls, N.Y. Salary $10,000 a Year, full maintenance with house and automobile furnished. Bed capacity–48.

MEDICAL OFFICER: Glenn Dale Sanatorium, the D. C. tuberculosis hospital. Salary range, $7040 to $8040 per annum. Sick and annual leave and retirement benefits under U. S. Civil Service. One year's approved training in pulmonary diseases and eligibility for D. C. license required. Overtime pay for work in excess of 40 hours per week. Address inquiries to Superintendent, Glenn Dale Sanatorium, Glenn Dale, Md.

STAFF PHYSICIANS: 700-bed, modern state tuberculosis hospital, located in town 25,000. Experience not essential. Eligibility North Carolina license desired. Salary depends on qualifications. Apply Medical Director, Eastern North Carolina Sanatorium Wilson, N.C.

POSITIONS WANTED

Experienced Administrator and Chest Specialist desires superintendency or medical directorship in a tuberculosis hospital. Outstanding qualifications. Excellent references from chest specialists of national repute. Box 130, American Review of Tuberculosis, 280 Madison Avenue, New York 16, N. Y.

Now Available in Spanish

Clasificación y Diagnóstico Standard

(DIAGNOSTIC STANDARDS)

First published by the National Tuberculosis Association in 1950 and now in regular use by more than 100,000 physicians, this accepted authority on terminology, standard tests and classification in tuberculosis has now been translated into Spanish by Professor H. Orrego Puelma of the University of Chile Faculty of Medicine, assisted by Doctors Raul F. Vaccareza, Ignacio Baldo and Armando Alonso, and is available to interested physicians in the form of a 64-page publication.

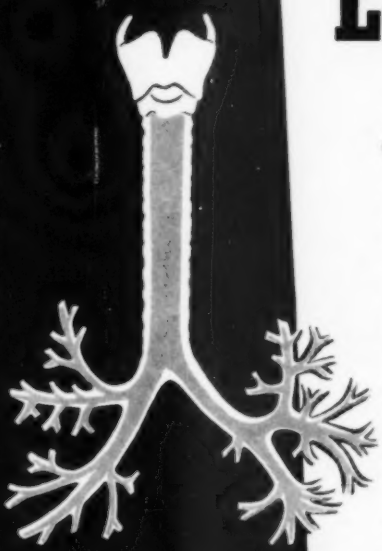
To cover handling costs, a price of 50 cents (American funds or the equivalent) has been established. Your order is cordially invited and will have immediate attention.

Please address orders to:

DR. H. ORREGO PUELMA

Hospital del Salvador,

58½ Vicuna Mackenna, Santiago, Chile.



spotlights
the bronchial tree

well-tolerated contrast medium

LIPIODOL*

for definitive diagnosis
of bronchopulmonary lesions

bronchiectasis "... definite demonstration ... is best accomplished by the instillation of *iodized oil* (Lipiodol) into the bronchial tree."[1]

chronic pneumonitis "An absolute diagnosis rests upon (1) x-ray, (2) Lipiodol bronchial visualization, and (3) bronchoscopy."[2]

lung abscess "Lipiodol bronchography has an important function in chronic abscess to reveal hidden cavities. ..."[3]

1. Meakins, J. C.: The Practice of Medicine, ed. 5, St. Louis, The C. V. Mosby Company, 1950, p. 154.
2. *ibid.*, p. 268.
3. Bishop, P. A., and Lindskog, G. E.: Lung Abscess, in Pillmore, G. U.: Clinical Radiology, Philadelphia, F. A. Davis Company, 1950, vol. 1, p. 339.

*Lipiodol (Iodized Oil, U.S.P.) is the registered trademark for the original product created by Lafay and is the only iodized oil meeting the specifications of the U.S.P. This product alone can bear the name Lipiodol.

FOUGERA

E. FOUGERA & CO., INC., 75 VARICK ST., NEW YORK 13, N. Y.
Canadian Distributors: Vinant, Ltd., Montreal, Canada.

Copyright, 1953, E. Fougera and Company, Inc.

The singing child on this year's Christmas Seal is a symbol of hope and faith in the future, and a pledge to the present.

The *hope* is the eventual eradication of tuberculosis . . . the *faith* is in the proved methods of your national, state, and local tuberculosis associations.

The *pledge* is your joining with 13,000,000 of your fellow Americans who this year will buy and use Christmas Seals.

Contribute today and join in singing to all humanity, to all the world, "Happy Christmas, Little Friend."

Buy Christmas Seals

a new advance in the control of tuberculosis

Drug therapy for the management of tuberculosis continues to advance at a rapid pace. In keeping with the latest improvement—which promises a substantially lower incidence of vestibular and auditory toxicity—Pfizer has made available a new combination of streptomycin and dihydrostreptomycin—

Combistrep*

STREPTOMYCIN AND DIHYDROSTREPTOMYCIN COMBINATION

Recent clinical studies[1] have shown that such a combination, one-half streptomycin and one-half dihydrostreptomycin, gave rise to a significant reduction in neurotoxic side effects as compared to equivalent dosage of either drug used alone, even though administered over the prolonged treatment periods required for the control of tuberculosis.

Combistrep offers these benefits to the tuberculous patient with the further assurance that its purity is of the same high standard typical of all Pfizer pharmaceuticals.

Available in vials of 1 Gm. and 5 Gm., dry powder for preparation of solutions for intramuscular injection.

1. Heck, W. E.: Reduced Ototoxicity by Combined Streptomycin-Dihydrostreptomycin Treatment of Tuberculosis, Scientific Exhibit 317, 102nd Annual Meeting A.M.A., New York, June 1-5, 1963.

also,

Streptomycin Sulfate—dry powder and solution

Dihydrostreptomycin Sulfate—dry powder and solution

Streptohydrazid*—a crystalline compound combining streptomycin and isoniazid

Cotinazin®—brand of isoniazid

Viocin* Sulfate—brand of viomycin, for resistant cases of tuberculosis

Pfizer

Pfizer Laboratories, DIVISION, CHAS. PFIZER & CO., INC., BROOKLYN 6, N.Y.

*TRADEMARK

Professional Films

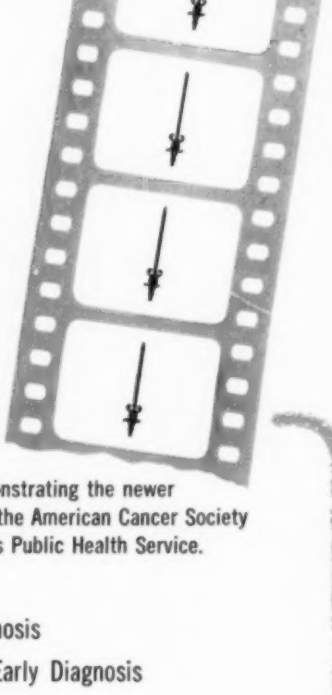
for

Hospital Staff Conferences

Medical Schools

Postgraduate Refresher Courses

State and County
Medical Society Meetings



A distinguished series of color films graphically demonstrating the newer diagnostic techniques in cancer. Sponsored jointly by the American Cancer Society and the National Cancer Institute of the United States Public Health Service.

Cancer — The Problem of Early Diagnosis

Breast Cancer — The Problem of Early Diagnosis

Gastrointestinal Cancer — The Problem of Early Diagnosis

Uterine Cancer — The Problem of Early Diagnosis

Oral Cancer — The Problem of Early Diagnosis

Lung Cancer — The Problem of Early Diagnosis (In production for winter release)

All are 16 mm. sound films in color

As a service to the medical profession, showings of these and other teaching films in our Professional Film Loan Library will be arranged by the Division of the American Cancer Society in your state upon request.

American Cancer Society, inc.

47 Beaver Street, New York 4, New York

Viomycin* Sulfate

"a third potent tuberculostatic agent"[1]

now available as **Vinactane**T.M. **Sulfate**

Viomycin Sulfate Ciba

- Active even when bacillary resistance to streptomycin or isoniazid has developed
- Side effects rare and generally mild in therapeutic dosage
- Especially recommended in combination with PAS or other antituberculous antibiotics

Supplied as sterile vials: The equivalent of 1 Gram viomycin base as the sulfate.

1. Hobby, G. L., Lenert, T. F., Rivoire, Z. C., Donikian, M., and Pikula, D.: Am. Rev. Tubere. 67:808, 1953.

Detailed literature sent on request of physicians

Ciba Pharmaceutical Products, Inc., Summit, N. J.

*Isolated in Ciba Research Laboratories

Ciba

2/1024M

New NTA Publication

Pennsylvania Pioneers

AGAINST

Tuberculosis

By Esther Gaskins Price

294 Pages *Cloth Bound* *$5.00 a Copy*

In this fully documented volume, there are brought together for the first time the stirring facts about the inception, development, and fruition of one of the most successful health crusades in history.

When this crusade started, tuberculosis was claiming human lives at the rate of more than 20,000 in a single decade in Philadelphia alone. Popular superstitions, medical conservatism, the hostility of landlords, industrialists and politicians, were some, but by no means all, of the difficult road blocks which confronted the pioneers.

Original Sources

Utilizing the proceedings of some of the most important medical meetings of the 19th century—the archives of the Pennsylvania Tuberculosis and Health Society and public health departments, newspaper files, and family records—PENNSYLVANIA PIONEERS AGAINST TUBERCULOSIS gives the historic details of the long drawn out battle waged by pioneers in the tuberculosis control movement.

This battle, spearheaded by Lawrence Flick and a small but forward-thinking group of earnest co-workers, finally led, among many other specific results, to the creation of the original tuberculosis society in the United States and the establishment of the first institution in medical history to concentrate on the prevention and treatment of a single illness.

Readers of the American Review of Tuberculosis will find in this book interesting and valuable background data, never before available, covering the critical period in which effective health control measures first began to assume their present shape.

Send your order today to:

National Tuberculosis Association, 1790 Broadway, New York 19, N.Y.

Additional postage outside U.S. and Canada, 50 cents a copy.

IN TB CHEMOTHERAPY

NEW "DOUBLE THREAT"

Dosage Equivalents		
BUFFERED 'PARASAL'-INH Total Daily Tablets	YIELDS PAS	TOTAL DAILY + Isoniazid
24	12 Gm.	+ 300 mg.
18	10 Gm.	+ 250 mg.
10	9 Gm.	+ 225 mg.
16	8 Gm.	+ 200 mg.

40% FEWER TABLETS

17 BUFFERED PARASAL-INH tablets replace 28¼ tablets (24 Sod. PAS 0.5 Gm. plus 4¼ INH 50 mg.) . . .

GREATER ECONOMY AND CONVENIENCE.

Because far fewer tablets are required, medication cost is correspondingly low . . .

VIRTUALLY PREVENTS GI:!

The unique *buffer* incorporated in each tablet virtually prevents GI upset — even in cases intolerant to ordinary Sodium PAS and INH taken separately.

SODIUM AND SUGAR-FREE

BUFFERED 'PARASAL'-INH is an effective, well tolerated, *single dosage form* for combined PAS-INH chemotherapy. Uncoated tablets are rapidly absorbed.

Buffered

PARASAL-INH

Write for samples, literature, complete information.

THE Panray CORP.

340 CANAL STREET, N.Y. 13, N.Y.

Coughing your head off?

Hycodan

BITARTRATE (Dihydrocodeinone Bitartrate)

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY

whenever
COUGH THERAPY is indicated

young folks
old folks
in-between folks

Three forms available: Oral Tablets (5 mg. per tablet), Syrup (5 mg. per teaspoonful), Powder (for compounding). Narcotic blank required. Average adult dose, 5 mg.

Endo®

Literature? Write
Endo Products Inc., Richmond Hill 18, N.Y.